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## PHYSIOLOGY OF THE COLON

LAWRENCE M. LARSON, M.D.

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AND

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ROCHESTER, MINN.

The large intestine in most animals, including man, is generally regarded as possessing merely storage function similar to that of a catch basin so that defecation may take place at a convenient time. In other words, it is looked on as a fixed tube, or system of tubing, present mainly to transmit feces. Metchnikoff's claim that man at one time made use of his large intestine as a reservoir, enabling him to pursue his prey or run away from enemies without undergoing risk of stopping to evacuate the bowels, no doubt contains much truth. However, his belief that people can live without this portion of the intestine, and that of Lane,<sup>1</sup> Waugh<sup>2</sup> and others regarding intestinal stasis and other possible evils for which the colon can be responsible, have thrown this organ into disrepute and probably have discouraged extensive study of its physiology. It is true that individuals can live without the large intestine; that certainly is no proof of its uselessness. On the other hand, it is no doubt true that this organ is undergoing a process of evolution better to suit changing needs and fashions, a fact which especially emphasizes itself in a consideration of present-day dietary standards. Under the conditions of living in the twentieth century, it is true that in certain instances the colon can be removed and not be missed, yet that does not prove that it is of no significance in human economy. It also may be possible that the organ has outlived its usefulness in the process of development of the body, but there can be no doubt that in lower animals its functions are definite and its loss is attended with serious results. However, in man, although to less extent, possibly, it has been proved that the colon can be removed without injury,

Abridgment of a thesis submitted by Dr. Larson to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery. Work done in Division of Experimental Medicine, the Mayo Clinic.

1. Lane, W. A.: *The Operative Treatment of Chronic Intestinal Stasis*, ed. 4, London, Henry Frowde, 1918.

2. Waugh, G. E.: *The Morbid Consequences of a Mobile Ascending Colon, with a Record of 180 Operations*, Brit. J. Surg. **7**:343 (Jan.) 1920.

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and there is no question as to the advisability of colectomy in such conditions as multiple diffuse polyposis.

From a study of the physiology of the large intestine it may be concluded that it is a bifunctional organ and, indeed, when one considers its embryologic development such a conclusion is obvious. Beginning low in the pelvis in the embryo and ascending upward in the median line, or slightly to the left, in the early months of fetal life the colon is a left-sided organ up to the splenic flexure, and it remains so in after-life, held in place by peritoneal fusion. From the splenic flexure, it festoons itself across the abdomen to another fixed point under the liver, arriving there at about the third or fourth month, whence it extends to the right iliac fossa to a semifixed situation in adults. This rotation around the superior mesenteric vessels is counterclockwise and constant, except in a small number of variants. In addition, the left half of the colon is developed from the hindgut, whereas on the opposite side it takes its origin with the small bowel below the papilla of Vater from the midgut, or the absorptive portion of the gastro-intestinal tract. This embryologic difference and the development of the proximal portion of the colon with the small bowel early called attention to the fact that there must be dissimilarity of physiologic function in the two halves, and the normal association of the proximal portion of the colon with the small bowel from the standpoint of physiology was readily established. Anatomic differences in conformation and construction in the two halves likewise indicated a difference of purpose. When pathologic processes developed, a study of them indicated that different types of lesions were found as a routine in the two arms of the colon, producing different symptoms. For example, a malignant lesion of the right side of the colon clinically called attention to itself by disturbances of the physiologic equilibrium, in sharp contradistinction to the obstructive phenomena characteristic of the distal part of the colon.

The cecum has long been regarded as a second stomach of primary significance in digestion and absorption, especially regarding cellulose in the herbivora; likewise, its enormous variation in size and appearance in various animals has been a subject of comment by many authors. It is regarded as of much shorter heredity than the small bowel and with a function which has been changing in the process of its evolution, so that definite statements regarding the physiology of this portion of the bowel cannot be made which hold true in all instances. In general, it may be stated, however, that the function of the right half of the colon is an absorptive one and that its movements are so regulated that progress of the food is slowed and thorough mixing is assured, thus favoring absorption. In the human being, very little digestion takes place here, although in some herbivora, especially in the horse, there is evidence that considerable takes place. The left portion of the large

intestine has a longer heredity; its functions are likewise more fixed, and in most animals it has been established that this portion acts more or less as a magazine for storage of residue. In general, the contents here are hard and more or less incompressible, whereas those of the right portion of the colon are semiliquid, so a rough division of the functional behavior may be made on this point alone. The mechanical activity of the two portions bears this out as the most distal part acts as a duct through which the contents are evacuated. It is thus seen that primarily the function here is propulsion and expulsion. Besides the motor and absorptive functions, the physiology of the colon includes that of secretion and excretion, the latter being no less important than the others and no doubt linked up with the elimination of poisons and toxins, as well as with the formation of the normal secretions of the colon.

#### MOVEMENTS OF THE PROXIMAL PORTION

The movements of the large intestine have been investigated by many writers, yet there are many points which still remain unsolved. Researches in this field have been conducted from many angles of approach, such as by the use of an abdominal window, by isolated strips of bowel, by observing the effect of section of nerves, by the use of various diets, by the action of drugs and by the use of pressure methods, such as balloons, and in recent years the use of the roentgen ray with a contrast medium has been invaluable in the study of the physiology of the colon.

After the introduction of roentgenoscopic methods in 1896, attention was drawn to many misconceptions in the field of gastro-enterology and, in a great number of cases, conditions which had formerly been considered anatomic variations were found instead to be normal physiologic movements; consequently, numerous revisions of the concepts of functions of the small and large intestines were necessary.

The first extensive study of the movements of the large bowel seems to have been made by Cannon<sup>3</sup> in 1902, who, by means of the roentgen ray, traced an opaque meal consisting of bismuth subnitrate mixed with salmon through the alimentary tract of the cat. Valuable deductions were made. In the cecum of the animal he found the most common movements to be antiperistalsis, as contrasted to the tonic rings of contraction and propulsive waves in the descending portion of the colon. These waves, he noticed, followed one another like those of the stomach, beginning either at the more advanced portion of the content in the colon or at the nearest tonic constriction, which he observed was frequently found at the termination of the transverse segment of the colon.

3. Cannon, W. B.: The Movements of the Intestines Studied by Means of the Röntgen Rays, *Am. J. Physiol.* 6:251 (Jan.) 1902.

The first sign of activity was an irregular undulation of the walls of the organ; then faint constrictions passed backward to the cecum. They usually appeared at first only in the region of the ascending colon, but often started near the end of the transverse segment and passed without interruption to the tip of the cecum, where new waves of peristalsis were inaugurated, and these waves finally succeeded in carrying food to the distal transverse colon. The activity was periodic with gradual disappearance of movements in a manner similar to that in which they appeared. Such a period of antiperistalsis lasted usually from four to five minutes and it was repeated at varying intervals, often from three to six times an hour. About twenty-five waves affected any one particle of food so that the result was a thorough mixing of contents, favoring close contact with the absorbing surfaces. These waves in the proximal part of the colon were definitely influenced by psychic factors. Cannon<sup>3</sup> inhibited these movements by holding the cat's nose so it could not breathe, and this in time stopped the movements altogether. There was no cessation of contractions during sleep; likewise, the movements continued during the night. Jacobj,<sup>4</sup> in 1890, seems to have been the first to recognize antiperistaltic movements in the colon, and although he did not describe them in detail, he did state that they seemed to originate from a more or less broad constriction ring. He used cats in which he produced colchicum poisoning, and his studies were made primarily on the small bowel.

Elliott and Barclay-Smith,<sup>5</sup> in a thorough study of antiperistalsis, using etherized animals under saline baths and injecting pea soup into the segments of bowel studied, made observations which in general agreed with those of Cannon. They also classified the different movements of the colon in a manner to explain the varying morphologic differences of that part of the alimentary tube in various mammals. Such difference, they stated, is related to habits of diet and not necessarily to zoologic classification. In the cat they found antiperistalsis, or backward-running waves of constriction, inherent throughout the length of the colon, and not confined to its proximal portion; yet, as a rule, this regressive movement was rarely present except in the ascending, transverse and cecal segments. In the herbivorous animals, such as the guinea-pig and rabbit, in which, as Starling<sup>6</sup> noted, a large part of the process of digestion and absorption goes on in the proximal portion of the colon, the latter is adapted for this, being capacious, with

4. Jacobj, Carl: *Pharmakologische Untersuchung über das Colchicumgift*, Arch. f. exper. Path. u. Pharmakol. **27**:119 (April 10) 1890.

5. Elliott, T. R., and Barclay-Smith, E.: *Antiperistalsis and Other Muscular Activities of the Colon*, J. Physiol. **31**:272 (June 30) 1904.

6. Starling, E. H.: *Principles of Human Physiology*, ed. 4, Philadelphia, Lea & Febiger, 1926.

big absorbent flaps of mucous membrane projecting into its interior. In the guinea-pig, these form a valve between the cecum and the proximal half of the colon which can resist a pressure of several inches of water seeking exit to the colon, but which yields readily to fluid moving with the current of antiperistalsis.

In Elliott and Barclay-Smith's studies on the dog, they never saw antiperistalsis, although the cecum contracted often and with apparently great force, but it did this with complete independence of movements in the other portion of the colon. They consider the cecum in the dog nonfunctional and dwindling, and that the current that has produced it has disappeared. This, in general, is in agreement with Bayliss and Starling's <sup>7</sup> observations, who considered the motor activity of the dog's colon as peristaltic; similar studies by Zondek <sup>8</sup> and also by Lurje <sup>9</sup> on the cat, rat, guinea-pig and other mammals confirmed Elliott and Barclay-Smith's results. Templeton and Lawson,<sup>10</sup> in their studies on the movements of the large intestine of the dog, by a system of balloons, were unable to detect any contractions which they could classify definitely as antiperistaltic.

In 1909, Cannon <sup>11</sup> again carefully studied the movements of the colon and, in corroborating his former observations, attempted to explain the origin and mechanism of antiperistalsis. He regarded the presence of tonic rings of constriction as of significance in the initiation of both peristaltic and antiperistaltic contraction, in substantiation of findings described by Biedermann <sup>12</sup> in 1904. He designated these tonic waves, in the colon as well as in the small bowel, as a persistent shortened condition of the musculature and suggested that it was due to continued excitation. Cannon,<sup>13</sup> in 1911 and 1912, reported further work along this line and emphasized the importance of internal pressure in its influence on movements of the colon. With the presence of a tonic ring

7. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, *J. Physiol.* **24**:99 (May 11) 1899; The Movements and the Innervation of the Large Intestine, *ibid.* **26**:107 (Dec. 31) 1900.

8. Zondek, B.: Study of Peristalsis, *Arch. f. Verdauungskr.* **27**:18, 1920; *abstr.*, *J. A. M. A.* **76**:346 (Jan. 29) 1921.

9. Lurje, H. S.: Untersuchungen über die motorische Funktion des Dickdarms: IV. Untersuchungen am überlebenden Dickdarm, *Arch. f. d. ges. Physiol.* **212**:64, 1926.

10. Templeton, R. D., and Lawson, H.: Studies in the Motor Activity of the Large Intestine: I. Normal Motility in the Dog, Recorded by the Tandem Balloon Method, *Am. J. Physiol.* **96**:667 (March) 1931.

11. Cannon, W. B.: Further Observations on the Myenteric Reflex, *Am. J. Physiol.* **23**:xxvi, 1908-1909.

12. Biedermann, W.: Studien zur vergleichenden Physiologie der peristaltischen Bewegungen, *Arch. f. d. ges. Physiol.* **102**:475 (May 21) 1904.

13. Cannon, W. B.: The Relation of Tonus to Antiperistalsis in the Colon, *Am. J. Physiol.* **29**:238 (Dec.) 1911.

of contraction, the internal pressure on adjacent parts of the intestinal wall is raised, the contraction regions nearby thus being distended and stimulated, with waves passing in each direction. However, he explains that as the contents of the colon are more viscous as they approach the median portion, so in the presence of a tonic ring, with fluid on one side and a viscous mass on the other, the effect would be different. On the side of the latter, the ring could not distend the wall and the wave would not pass distally, but proximally (antiperistalsis). The distal content could be moved by a contraction of the ring, and this is what Elliott and Barclay-Smith saw in the rat and other animals. If the contents were soft, the movements were likely to be antiperistaltic, but if the contents were dry and hard, peristalsis was the usual result, thus showing that the consistence of the feces was of significance in determining the type of movement present. The tonic ring of contraction was maintained after destruction of the spinal cord and, no doubt, the result of increased internal pressure. Balli<sup>14</sup> has enumerated seven definite situations in the colon which, in reality, are spastic areas, although he designated them as sphincters, and further stated that these are the points of origin of antiperistaltic and peristaltic waves. They are as follows: (1) in the ileocecal area; (2) between the cecum and the ascending colon; (3) in the cecocolic area in the proximal segment of the ascending colon; (4) in the transverse colon, at the juncture of its first and third portions; (5) at the splenic flexure; (6) at the juncture of the sigmoid and descending portions, and (7) between the sigmoid and the rectum. Other factors influence these waves, such as intestinal gases, and Henderson<sup>15</sup> has shown that the carbon dioxide content of the blood may be of importance to a certain extent in the activity of the bowel.

In 1918, Alvarez and Starkweather,<sup>16</sup> studying intestinal gradients of rhythmicity, irritability and metabolism, showed that these were present in the colon as well as in the small intestine. They suggested that the herbivora, with their rough, less easily digested, bulky foods and their thin-walled bowel, need a more even gradient than the carnivora. In the cat and the dog, the lower end of the gradient was often reversed, and this may save these animals from frequent calls to defecation. Accentuation of this reversal of gradient, they explain, may be present with some types of constipation.

14. Balli, R.: The Sphincters of the Colon, *Radiology* **12**:484 (June) 1929.

15. Henderson, Yandell: A Method for the Direct Observation of Normal Peristalsis of the Stomach and Intestines, *Proc. Soc. Exper. Biol. & Med.* **6**:67, 1908-1909.

16. Alvarez, W. C., and Starkweather, Esther: The Metabolic Gradient Underlying Colonic Peristalsis, *Am. J. Physiol.* **47**:293 (Dec.) 1918.

Meltzer and Auer<sup>17</sup> watched the intestinal movements through the shaved abdominal wall of the rabbit and saw peristaltic waves, but did not mention antiperistalsis; likewise, Alvarez<sup>18</sup> stated that in this animal peristaltic waves seem to be very rare.

Thomas and Kuntz<sup>19</sup> observed reversed movements near the cecum in a dog, and Lenz,<sup>20</sup> using a celluloid abdominal window in a cat, definitely established the presence of antiperistaltic waves, regarding them as movements of retention. Likewise, Basler,<sup>21</sup> in 1909, saw churning movements in rats and cats. Groves, in 1909, injected a colored fluid into the rectum of a boy with a cecal fistula and saw this fluid come from the fistula in jets every four or five minutes. It was not in a continuous stream, so he was strongly inclined to the view that antiperistalsis was responsible for the backward movement of this fluid. Smith-Shand<sup>22</sup> saw large antiperistaltic waves in the proximal portion of the colon in a case of obstruction of the colon at the sigmoid flexure, and Schwarz<sup>23</sup> saw a similar type of movement in a patient with chronic constipation.

Further evidence of the presence of antiperistaltic waves in the proximal portion of the colon has been substantiated by experiments in which reversal of a segment of the cecum or ascending portion of the colon has been done. This type of work is similar to that done on the small bowel in which these waves no doubt take place. In 1907, Beer and Eggers<sup>24</sup> reversed 6 inches (15 cm.) of ascending colon and obtained results similar to those found after a similar operation has been done on the small bowel; namely, peristaltic waves descend from the ileum across the upper anastomosis and then along the reversed loop but stop at the distal anastomosis. Circular contractions follow each other in the reversed loop in the same direction as normal peristaltic waves. Likewise, as in the small intestine, the reversed segment of

17. Meltzer, S. J., and Auer, John: Peristaltic Movements of the Rabbit's Cecum and Their Inhibition with Demonstration, *Proc. Soc. Exper. Biol. & Med.* **4**:37, 1906-1907.

18. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, New York, P. B. Hoeber, Inc., 1928.

19. Thomas, J. E., and Kuntz, Albert: A Study of Gastro-Intestinal Motility in Relation to the Enteric Nervous System, *Am. J. Physiol.* **76**:606 (May) 1926.

20. Lenz, E.: Observations à la fenêtre abdominale "colique" du chat: I. Mouvements intestinaux normaux et action péristaltogène des purgatifs anthraquinoniques, *Arch. internat. de pharmacodyn. et de thérapie* **28**:75, 1923-1924.

21. Basler, Adolf: Beiträge zur Kenntnis der Bewegungsvorgänge des Blinddarmhalses, *Arch. f. d. ges. Physiol.* **128**:251 (May 28) 1909.

22. Smith-Shand, A. K.: Antiperistalsis in the Large Intestine, *J. Roy. Nav. M. Serv.* **4**:367, 1918.

23. Schwarz, Gottwald: Zur Physiologie und Pathologie der menschlichen Dickdarmbewegungen, *München. med. Wchnschr.* **58**:1624 (July 25) 1911.

24. Beer, Edwin, and Eggers, Carl: Are the Intestines Able to Propel Their Contents in an Anti-Peristaltic Direction? *Ann. Surg.* **46**:576, 1907.

colon contains foreign bodies, and dilatation at the upper union takes place where the opposed peristaltic waves meet. Fluid material passes through the loop readily. It is believed that antiperistalsis takes place here, propelling the content of the loop onward, yet the results are not convincing since adaptability of the bowel to new conditions may explain the entire situation. In 1923, Muennich<sup>25</sup> studied antiperistalsis on excluded intestinal segments. He found (contrary to Roith's<sup>26</sup> opinion that antiperistaltic waves cease from the middle transverse portion of the colon downward) that they seemed to be present in the entire organ. He demonstrated a backward flow in cases of ileosigmoidostomy, thus explaining the filling up of the colon back to the cecum and no doubt resulting in the untoward symptoms seen in cases of this nature. Albrecht<sup>27</sup> reported a similar case, and likewise concluded that antiperistalsis in the excluded segment was the explanation of the phenomenon. Blamoutier,<sup>28</sup> in 1925, using roentgenoscopic methods, saw antiperistaltic waves in all portions of the colon except the rectum, and even occasionally noted them in this segment of the large intestine. Cannon,<sup>12</sup> in 1911, stated that reverse movements are present, and that retrogression of feces from the rectum may take place by this movement. It commonly occurs after repression of desire for defecation. However, the rectum may often be full of feces, as Alvarez<sup>18</sup> and other clinicians have found during examinations of the pelves of women, so that retrogression is not always the rule.

The possibility that antiperistaltic movements can be the cause of vomiting has been disputed. Beer and Eggers<sup>24</sup> and Nothnagel<sup>29</sup> stated that vomiting of formed feces and of enemas introduced into a normal gastro-intestinal tract cannot be explained on any other basis. Alvarez quoted a number of authors who have observed the stomach in vomiting and rarely have they observed reversed movements. Alvarez suggested that a general reversal of the intestinal gradient may occur in which the colon takes only a small part.

Colored substances have been injected into the rectum and the subsequent course watched. Bond, in 1905, showed that particles of carmine can travel from the anus back to the cecum and even higher by

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25. Muennich, G. E.: Unilateral Intestinal Exclusion, *Surg., Gynec. & Obst.* **36**:773 (June) 1923.

26. Roith, O.: Ueber die Peristaltik und Antiperistaltik des menschlichen Dickdarmes, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **25**:203, 1912.

27. Albrecht, Hans: Zur Frage der Antiperistaltik im Dickdarm bei schwerer Obstipation, *München. med. Wchnschr.* **59**:1592 (July 16) 1912.

28. Blamoutier, P.: Les mouvements antiperistaltiques du gros intestin, *Paris méd.* **55**:325 (April 4) 1925.

29. Nothnagel, C. W. H.: Beiträge zur Physiologie und Pathologie des Darmes, Berlin, A. Hirschwald, 1884.

"reverse currents." Grützner,<sup>30</sup> Nothnagel and Starling used similar methods, but their conclusions were against the presence of so-called reverse currents. However, their experiments were performed on dogs, and in these animals antiperistalsis probably does not occur, at least not to any considerable degree.

The introduction into the rectum of an enema, such as saline solutions, by means of the Murphy drip proctoclysis, is followed by transportation by antiperistalsis of the fluid to the proximal or absorbing portion of the large intestine, and explains the disappearance of large quantities of fluid introduced in this manner.

Roentgenographic studies on antiperistaltic movements in the colon of man have contributed much of value. Stierlin,<sup>31</sup> in 1910, and Stierlin and Fritzsche<sup>32</sup> saw reverse transport of feces in the colon of baboons but could detect no such activity in the large intestine of man. Kaestle,<sup>33</sup> in 1912, Serena,<sup>34</sup> in 1913, and Guarini,<sup>35</sup> in 1919, were of the same opinion, after making studies of a similar nature. Schwarz,<sup>36</sup> in 1911, found contractions occurring in an anal as well as an oral direction, but could not determine which were most pronounced. Hertz and Newton,<sup>37</sup> in 1913, by filling the colon with an average-sized opaque enema, saw the fluid run passively to the cecum but with a slight excess. Contractions were stimulated, and the fluid passed in both directions from contracting segmental rings. The latter were associated with a desire to defecate. In agreement with Walsham and Overend<sup>38</sup> and Isémein and Poinso,<sup>39</sup> they were still in doubt as to whether these waves were antiperistaltic.

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30. Grützner, P.: Ueber die Bewegungen des Darminhaltes, *Arch. f. d. ges. Physiol.* **71**:492 (May 4) 1898.

31. Stierlin, Eduard: Ein Beitrag zur radiographischen Untersuchung der Kolonperistaltik, *Ztschr.f.klin.Med.* **70**:370, 1910.

32. Stierlin, Eduard, and Fritzsche, E.: *Verhandl. d. deutsch. Kong. f. inn. Med.* **29**:183, 1912.

33. Kaestle: Die Bewegungsvorgänge des menschlichen Dünn und Dickdarmes während der Verdauung auf Grund röntgenographischer und röntgenkinematographischer Untersuchungen, München. med. Wchnschr. **59**:446 (Feb. 20) 1912.

34. Serena, M.: Studio dei piccoli movimenti del colon col seriografio, *Atti d. Cong. ital. di radiol. med.* **1**:161, 1913.

35. Guarini, C.: Osservazione di movimento colico, *Radiol. med.* **6**:99, 1919.

36. Schwarz, Gottwald: Zur genaueren Kenntnis der grossen Kolonbewegungen, München. med. Wchnschr. **58**:2060 (Sept. 26) 1911.

37. Hertz, A. F., and Newton, Alan: The Normal Movements of the Colon in Man, *J. Physiol.* **47**:57 (Oct. 17) 1913.

38. Walsham, Hugh, and Overend, Walker: On the Movements of the Colon, *Arch. Radiol. & Electroth.* **20**:260 (Dec.) 1915.

39. Isémein, Léon, and Poinso, Robert: Physiologie des côlons, *Gaz. d. hôp.* **97**:897 (July 5) 1924.



Lenz,<sup>40</sup> in 1919, noted a retrotransport of feces in the colon of man due to a strongly active contraction directed orally, but he did not consider this as identical to antiperistalsis. Case<sup>41</sup> stated that reversed waves are the prevailing type of movement in the proximal colon and that they may become exaggerated in the presence of obstruction lower, thus resulting in stasis in the proximal segment. He called attention to the fact that many writers have described gangrene of the cecum associated with obstruction in the pelvic or sigmoid portions of the colon, and explained the phenomenon as due to waves of antiperistalsis originating at a tonic contraction ring creating back pressure, resulting in distention of the cecum. Blamoutier,<sup>42</sup> in 1925, definitely saw this type of contraction ring from which waves of antiperistalsis seem to arise. He commented on the fact that the ileocecal valve would soon atrophy if it were not for the presence of reverse waves.

Movements other than antiperistalsis take place in the proximal colon. Cannon<sup>43</sup> stated that there are several of these, the first of which he called the serial sectioning movement. This consists of the separation of a small segment in the cecum by a constriction, followed by a second constriction which cuts off another segment just above the first, and with the disappearance of the first constriction, the separated segments unite. A third segmentation then takes place above the second and the changes again occur, thus sectioning the whole mass. Another movement consisting of broad constricting bands appearing and relaxing results in a gentle kneading of the contents. He also noted other movements in the ascending colon, such as strong constricting rings, forcing the contents into the transverse colon. Sometimes these started at the ileocecal valve, but more often they originated in the ascending portion, usually without visible stimulation. Elliott and Barclay-Smith found what they called "propulsive peristalsis" which was present throughout the colon in the animals they studied and which was responsible for the downward movements of the contents.

Holzknacht's<sup>43</sup> opinion was that the colon of man rests most of the time and is active only three or four times each day. He saw masses of feces pass through the colon for a considerable distance almost instantaneously and called them "mass movements."

40. Lenz, Emil: Der retrograde Transport im Dickdarm des Menschen, sein Wesen, seine physiologische und klinische Bedeutung, *Arch. f. Verdauungskr.* 25: 54 and 128, 1919.

41. Case, J. T.: Surgical Physiology and Pathology of the Colon from the X-Ray Standpoint, *New York State J. Med.* 21:156 (May) 1921.

42. Cannon, W. B.: Peristalsis, Segmentation and the Myenteric Reflex, *Am. J. Physiol.* 30:114 (April) 1912.

43. Holzknacht, G.: Die normale Peristaltik des Kolon, *München. med. Wchnschr.* 2:2401 (Nov. 23) 1909; The Normal Peristalsis of the Colon, *Arch. Roentgen Ray* 14:273 (Feb.) 1910.

These belong more properly to movements of the left half of the colon and will be considered later. Stierlin<sup>31</sup> found that the cecum possessed the least motor capacity of any portion of the colon. Schwarz, in his fluoroscopic work on the large intestine, found that the latter was never at rest but was continually moving and at times capable of very intensive, rapid contractions, leading to considerable displacement of its content toward the anus. The observations of Kaestle, Hertz and Newton, Case, Walsham and Overend, Hertz,<sup>44</sup> Lenz,<sup>40</sup> Lignac,<sup>45</sup> Guarini, Isémein and Poinso, and Blamoutier are of similar nature.

In summarizing the movements of the proximal portion of the colon, it may be stated that this segment is a mixing and absorbing one, and the movements here are not so pronounced or well defined as in the remainder of the large intestine, which is the propelling segment.

*Functions of the Haustra and Taeniae.*—At this point, it may be well to consider the functions of the haustra. Lineback<sup>46</sup> has made the most recent and most extensive studies on the subject. On the outer surface of the colon there are three lines of thickening of the longitudinal muscle layer called the taeniae, which are well defined in the adult. These are shorter than the colon; so they have the property of decreasing its length and thus causing the intervening parts of the intestinal wall to be drawn or puckered into folds called haustra. Kaestle<sup>33</sup> and Katsch<sup>47</sup> think these folds may be produced by the local constriction of circular fibers, but it is probably true that both factors operate to produce the condition. Lineback, corroborating Lowitz's<sup>48</sup> observations, showed that many small bundles of fibers pass from the longitudinal layers to the circular layers, so that the latter are somewhat thinned in the region of the taeniae. By roentgen studies he noted that the waves of contraction in the circular muscle which produce clefts in each of the three regions between the taeniae occur independently, and rarely do two clefts or zones of contraction occur exactly opposite each other on each side of the taeniae. The effect is usually limited to one region between the taeniae. This is due mainly to the fact that the circular fibers are not strong enough to draw down the taeniae into a

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44. Hertz, A. F.: Constipation and Allied Disorders, London, Henry Frowde, 1909.

45. Lignac, Pierre: Les mouvements rétrogrades du colon et leur étude radiologique, Presse méd. **27**:52 (Jan. 30) 1919.

46. Lineback, P. E.: Studies on the Longitudinal Muscle of the Human Colon, with Special Reference to the Development of the Taeniae, Contrib. Embryol. **11**: 35, 1920.

47. Katsch, Gerhardt: Der menschliche Darm bei pharmakologischer Beeinflussung seiner Innervation, Fortschr. a. d. Geb. d. Röntgenstrahlen **21**:159, 1914.

48. Lowitz, G. A.: Recherches sur l'appareil musculaire du gros intestin chez l'homme et quelques mammifères, Thèse de Bordeaux, no. 41, 1896, p. 32.

cleft and the latter, therefore, act more or less as strong, fixed, longitudinal cables on which the former pull. Thaysen,<sup>49</sup> in 1916, by roentgen studies, found that the shape of the haustra could be altered by the finer contractures of the circular muscles within them. Courtade and Guyon,<sup>50</sup> studying both of these layers, concluded that the inferior mesenteric nerve principally controlled the circular muscle, and the sacral nerve the longitudinal muscle, which confirmed Biedermann's<sup>51</sup> work, suggesting separate nerve control of the two layers.

Kaestle studied the function of the haustra minutely in his fluoroscopic work on the colon of man, especially those in the proximal portion, and showed that here the food is thoroughly kneaded and mixed by their alternate broadening and narrowing. He also observed complete contraction of the haustra, either singly or simultaneously in groups, concluding that the occurrence of deep haustration was physiologic and emphasizing that it was not a spastic phenomenon. He also saw changes in positions of the haustra due to narrowing and widening of the colon over varying lengths, and in the distal part of the colon haustral processes were not so complicated although invaginations and bulgings were observed, as well as segmentation of spherical balls of feces. Hertz and Newton compared the haustral movements to segmentation of the small bowel, and Case, and Howell<sup>52</sup> found them almost constantly in action, mixing materials and aiding in propelling the contents onward. Rutherford<sup>53</sup> observed in a patient with a fistula of the cecum that a haustrum grasped a small, moist mass of feces, enveloped it, and then retained it until dry; when it was pushed back into the lumen of the bowel.

*Mechanism of Peristalsis in the Colon.*—The mechanism by which movements of the digestive tract, as well as those of other involuntary muscles, take place has been carefully worked out by a number of investigators, but with by no means conclusive results. It has been well established that rhythmic contraction is an inherent property of muscle and muscle-like tissue, which fundamentally is brought about by recurring cycles of chemical activity, and no doubt these are myogenic in origin, although they can be stimulated and coordinated by

49. Thaysen, T. E. H.: Ueber den Bau und die Entstehung der Haustra coli, Anat. Hefte 54:321, 1916-1917.

50. Courtade, D., and Guyon, J. F.: Innervation motrice du gros intestin, Compt. rend. Soc. de biol. 49:745, 1897.

51. Biedermann, W.: Zur Physiologie der glatten Muskeln, Arch. f. d. ges. Physiol. 45:369, 1889.

52. Howell, W. H.: A Text-Book of Physiology, ed. 10, Philadelphia, W. B. Saunders Company, 1927.

53. Rutherford, A. H.: The Ileocecal Valve, New York, P. B. Hoeber, Inc., 1914.

nerves and nerve plexuses. In the bowel this is done especially by Auerbach's plexus which is attached to the longitudinal coat and communicates outside the bowel by the extrinsic nerves. Whether these movements downward are explainable according to Bayliss and Starling's<sup>7</sup> law of the intestine, to Keith's<sup>54</sup> theory of nodes or to Alvarez's gradient idea is not yet proved. The happenings in the gastro-intestinal tract are readily explained by the presence of gradients, and Alvarez conceived of a number of these as present, such as of pulling force, of tone, of rhythmicity and of irritability, although he considered the fundamental and underlying gradient metabolic, and gave logical and clearcut explanations.

There have been many explanations regarding the mechanism by which the movements of the colon take place. Bayliss and Starling,<sup>7</sup> in 1901, saw contractions in the dog pass from the ileum directly on over to the large intestine, and these were present also after complete enervation of extrinsic nerves. Alvarez, however, considers the ileo-cecal sphincter a barrier to most of the movements as well as to the contents of the ileum, although he saw a few waves pass on down into the colon in a rabbit. He presented evidence showing that by the folding of the muscle layers this leads approaching waves into a blind pocket where they are lost. This is in agreement with Luciani's<sup>55</sup> observation that peristalsis of the colon is usually not a continuation of that of the small bowel. Alvarez and Starkweather show that irritability in the cecum is low, probably due to the poor development of Auerbach's plexus here, which accounts for the fact that it acts so well as a reservoir and is little influenced by movements elsewhere in the digestive tract. Many cases of so-called cecal stasis have been attributed to defects in Auerbach's plexus, as well as to the position of the colon and to maldevelopments.

Bayliss and Starling considered inhibition to take place below the point of stimulation in the large as well as in the small bowel, and the same inhibitory effect to take place below a descending peristaltic wave. They found it difficult to demonstrate an ascending type of excitation in the colon, as compared to the small bowel, but they concluded that the movements are under the control of a local nerve mechanism, and peristaltic waves are due to a combination of ascending excitatory and descending inhibitory impulses. Their opinion was that these usually started in the local nerve plexuses due to the presence of a stimulating agent in the lumen of the bowel. Cannon<sup>13</sup> found a refractory period present during the period of shortening, similar to that found in the

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54. Keith, Arthur: Cavendish Lecture on a New Theory of the Causation of Enterostasis, *Lancet* 2:371 (Aug. 21) 1915.

55. Luciani, Luigi: *Human Physiology*, New York, The Macmillan Company, 1913, vol. 2.

stomach and small bowel. Elliott and Barclay-Smith, studying the mechanisms of antiperistaltic waves, presumed them to be immediate myogenic responses to distention and correlated them to the churning movements of the small bowel. Alvarez's gradient idea explains the phenomena of movements in the colon in a logical manner. The ileocecal sphincter normally has a gradient of irritability higher than that of the ileum, thus explaining backward reflection of waves over the ileum, the sphincter functioning as an effectual barrier. The muscle of the colon is more sluggish than that of the ileum, and segments of the tip of the cecum were less irritable than those from the base. In studying the movements of the cecum, he found the gradient to be upward from the base of the cecum, through to the remainder of the colon, thus explaining its reservoir function. He showed that normally the tone of the rectum and sigmoid is higher than that of the colon immediately above; this he noted to be helpful in keeping fecal matter from packing up against the sphincter, and this explains how sometimes feces are returned to the upper part of the colon when defecation is postponed. Defecation can be readily supposed to take place when the gradient above becomes so steep or that of the sigmoid and rectum so lowered that the fecal material moves downward. In a similar manner, interference or an abnormal gradient may explain constipation, postoperative ileus, vomiting, gastric dilatation and dyspepsia.

*Studies of Movements of the Colon with Various Types of Enemas.*—The introduction of the opaque enema along with roentgenoscopy or fluoroscopy, and the use of other types of enemas, have afforded an important means of studying the physiology of the colon. Cannon,<sup>3</sup> in 1902, made many observations, using roentgenographic methods, and thought that enemas in general stimulated antiperistalsis of the colon; the movements sometimes lasted over an hour, but usually they were not strong enough to force the contents through the ileocecal valve unless the enemas were very large. However, he once saw these waves in a normal subject, after using an extremely small enema, so came to no definite conclusions. In the cat a small enema of 25 cc. of the opaque mixture first lay in the descending colon; then reverse waves were soon set up and the material was forced back into the cecum, but nothing went through into the small intestine. With from 90 to 100 cc., it was often observed to pass through the ileocecal valve. Schwarz,<sup>23</sup> in 1911, found that considerable stimulation to contraction of the colon was obtained by use of various enemas, and his observations in human beings were similar to those of Drummond,<sup>56</sup> who noted that enemas rarely go beyond the cecum; in other words, the ileocecal valve was usually com-

56. Drummond, Hamilton: *Observations on the Functions of the Colon, with Special Reference to the Movements of Enemata*, Brit. M. J. 1:240 (Jan. 31) 1914.

petent. Hertz<sup>44</sup> found that if more than 750 cc. of fluid was used in human beings, the colon contracted and expelled the contents, and he thought that hydrostatic pressure alone brought about passage of fluid to the cecum. Drummond tried this on cadavers and found that the fluid passed backward just as rapidly as in the living person.

Joltrain, Baufle and Coope<sup>57</sup> produced pressure of various kinds in the large bowel and noted the effects. They found that the normal colon can hold about 1,000 cc. of fluid, which they computed was under a pressure of from 16 to 20 cm. height of water and created no distress. With various diseases of the large intestine the capacity was much less and the pressure under which it was retained was much greater. When the pressure rose to around 30 cm. of water, with a volume of 3,000 cc. in the colon, the patients complained of pain and distress. Burt<sup>58</sup> determined the pressure required to rupture the bowel at various levels by the introduction of air. He found the rectum to support the greatest average pressure, with the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum and stomach in order of their rupture. The greatest pressure supported was 11.59 pounds per square inch. In the rectum of a child, aged 11 years, and in adults, the average was around 8.36 pounds per square inch. The practical application of Burt's work lies in the emphasis of care in instrumentation in proctology, in administration of enemas and in the breaking up of impacted fecal masses. Friedenwald and Feldman,<sup>59</sup> in 1931, studied the detrimental effect of prolonged use of various enemas. Using tap water once daily for one hundred and fifty-five days, they saw a few hemorrhagic areas in two of three animals; with soap, only one of three had this appearance; with cotton seed oil, there were no changes, but with a solution of sodium bicarbonate, the typical clinical and pathologic picture of chronic ulcerative colitis was produced in each of the animals observed.

Betz found reflex contraction of the large intestine after the injection of a glycerin enema as high as the hepatic flexure, and Alvarez's view is that many times the effect may go much further. He voiced the experience of others in noting that patients occasionally become nauseated from ordinary injections of physiologic solution of sodium chloride and vomit when anything a little more irritating is introduced, such as soap, glycerin, turpentine or dextrose. This also gives founda-

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57. Joltrain, E.; Baufle, P., and Coope, R.: *Essai de mesure de la pression du gros intestin. Ses variations. Application a la clinique*, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:211, 1919.

58. Burt, C. A. V.: *Pneumatic Rupture of the Intestinal Canal with Experimental Data Showing the Mechanism of Perforation and the Pressure Required*, Arch. Surg. **22**:875 (June) 1931.

59. Friedenwald, J., and Feldman, M.: *Experimental Studies on the Effect of Prolonged Use of Colon Enemas upon the Bowels in Animals*, Am. J. Surg. **11**: 23 (Jan.) 1931.

tion for the opinion that part of the nausea and distress, and even of the vomiting, following abdominal operations may be due to the use of the Murphy drip type of apparatus for rectal instillation of fluids, and, in fact, several authors have commented on this. Rolleston and Jex-Blake<sup>60</sup> noted that in a series of ninety-six patients with gastric disturbances who were fed by rectum, twenty-six vomited at some time or other, and Bine and Schmoll<sup>61</sup> advised against the use of enemas in the presence of fecal vomiting, because in this condition any fluids instilled in the rectum would be liable to be vomited. The explanation of the phenomenon, as Alvarez stated, is a reversal of the normal gradient, with waves traveling in the opposite direction, due to the stimulation of the lower end of the tract by the irritating enemas.

The movements of the colon were studied by the authors with a tandem set of three balloons in the isolated large intestine of the dog. In this type of preparation in which nearly normal conditions were maintained, the ileum was connected to the sigmoid as closely as was anatomically possible and the two ends of the colon were brought out as in cecostomy and sigmoidostomy, respectively. In this manner, the influence of anesthesia as well as operative trauma could be excluded. Kymographic tracings were made of the movements by the use of small balloons connected to a water manometer system. The position of the balloons as checked at postmortem examination was found to be in the cecum, at the splenic flexure and in the lower part of the sigmoid. By administration of various cathartics through the stomach, definite activity could be elicited in this isolated loop such as that accompanying defecation, vomiting or the gastrocolic reflex.

One of the most evident facts that impresses one in this study is the marked difference in activity between the cecum and the remainder of the colon. The cecum was constantly active and from these movements of mixing and churning it could easily derive its important function of absorption. Whether these contractions are antiperistaltic or peristaltic, or whether they are the result of local stimulation was difficult to determine, but at any rate they were definitely of different character than those of the distal portion of the colon. They seem to represent a higher degree of irritability than is found elsewhere in this organ. Normally the distal part of the colon was almost completely inactive, showing only small, almost imperceptible contractions which probably were the effect of respiration. However, when activity did take place the most frequent movements were systolic pulsations and not peristaltic waves. The latter type of contraction was rarely definitely identified.

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60. Rolleston, H. D., and Jex-Blake, A. J.: On the Occurrence of Vomiting During Rectal Alimentation., *Brit. M. J.* **2**:68 (July 11) 1903.

61. Bine, René, and Schmoll, Emile: The Treatment of Gastric and Duodenal Ulcer, *California State J. Med.* **12**:361 (Sept.) 1914.

Many authors have found the colon never inactive but continually showing some degree of motility. These movements of the large intestine indicate a high degree of efficiency which has been developed, and show the adaptations of this organ to mechanical conditions which are present. The activity of the cecum promotes absorption and aids in retaining the fecal material until the consistence is such that it acquires form and is then pushed on though the transverse colon to the splenic flexure. From here it is transported by coarser movements and undergoes little change until it is expelled. Disturbances in this absorptive or expulsion function, such as retaining the feces in a liquid state throughout, or on the other hand, drying them too much, may account for some cases of diarrhea and of constipation, as many authors have suggested.

It is a common clinical observation in patients with diarrhea that after eating there are abdominal distress, cramps and the urge to evacuate the bowels, and also that the patient is definitely more comfortable between meals. There seems to be no doubt that there is a definite relationship between the ingestion of food and defecation in both normal human beings and animals. In the present series of experiments on the so-called gastrocolic reflex, the latter was definitely elicited in spite of the fact that there was lack of continuity in the intestinal tract between the stomach and colon, so that the possibility of an impulse running down the bowel by either neurogenic or myogenic means to stimulate the colon must be eliminated. In this connection, Alvarez quoted Short,<sup>62</sup> who noticed that the coils of the ileum were always active except during fasting, but when food was taken little gushes of succus entericus appeared at the ileocecal sphincter in from one and a half to four minutes. Likewise Cannon,<sup>13</sup> in 1911, showed that as food enters the cecum a fresh series of waves is initiated there. Lyman<sup>63</sup> further demonstrated what he called a "receptive relaxation" of the colon when food entered it from the ileum, similar to that of the cardia as its contents pass through the esophagus. He also noticed that as soon as the small bowel had finished emptying itself through the ileocecal sphincter and had again become quiet, the large intestine became active. His explanation is that there was reciprocal innervation of the two portions of the bowel. Surmont, Dubus and Tiberghien<sup>64</sup> sectioned the ileum near the cecum and could produce movements in

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62. Short, A. R.: Observations on the Ileo-Caecal Valve in Man, *Brit. M. J.* 2:164 (Aug. 9) 1919.

63. Lyman, Henry: The Receptive Relaxation of the Colon, *Am. J. Physiol.* 32:61 (May) 1913.

64. Surmont, H.; Dubus, A., and Tiberghien, P.: Contractions coliques consécutives à des excitations prépyloriques et duodénales, *Compt. rend. Soc. de biol.* 71:641, 1911.



the colon by irritation of the stomach. Likewise, Alvarez, in 1924, cut the bowel across and found that although no waves crossed this opening, yet simultaneous movements took place in many parts of the intestine, and he was of the opinion that nerves in the mesentery served to carry these impulses. The mechanism of the gastrocolic reflex he explained on a similar basis; this seems the most reasonable in accounting for the presence of this type of activity in the colon in this series of experiments.

#### MOVEMENTS OF THE DISTAL, OR LEFT, HALF OF THE COLON

The movements of the left half of the colon are antiperistalsis, which most investigators agree takes place, at times especially, in connection with a similar type of activity in the right half of the colon, and coordinated peristalsis, which drives the content onward, similar to that of the small bowel. Several other types of movements in the colon have been reported. The best understood of these are the strong contractures which evacuate the bowel. Elliott and Barclay-Smith noted that these were slow, powerful constrictions of the tube commencing at a point a considerable distance up the colon and running downward to empty the contents, an action common to all animals and a fundamental reaction to stimulation of the sacral nerves. Most of our knowledge of the movements of the colon has been gained by means of roentgenograms, either an opaque meal or an opaque enema being used.

Cannon,<sup>3</sup> in 1902, found that as the content from the proximal colon was pressed gradually onward toward the transverse and descending portion of the colon, a deep constriction appeared near the advancing end and almost separated a globular mass from the main body of food. The contents progressed farther along the colon, and new tonic constrictions appeared which separated the contents into globular masses. As these increased in number, they got farther from the cecum, although they were present chiefly in the descending colon. Raiser<sup>65</sup> recorded similar observations in the colon of the rabbit, in which deep circular constrictions separated the scybalous masses. Thus, as Cannon<sup>13</sup> brought out, these rings of constriction, moving slowly from the cecum, pushed the hardening contents before them. It is obviously an advantage to have them pushed through in divisions rather than in a uniformly cylindric mass, and while this is going on, some absorption takes place within the confines of these rings. Kaestle explained the facility with which the contents of the colon were moved forward as due to an advancing column of gas which opened up the lumen of the bowel before it.

65. Raiser, K. P. T.: Beiträge zur Kenntnis der Darmbewegungen (Giessen). Worms am Rhein, A. K. Boeninger, 1895.

Schwarz<sup>23</sup> added that increased abdominal pressure was of considerable significance in moving the fecal material along the colon, and that in constipation and in stenotic lesions of the bowel he could see the segmentation contractions somewhat accentuated, and even hypermotile, depending on the degree of occlusion of the lumen of the bowel. Serena, in 1913, made similar observations, and Bergmann<sup>66</sup> and Schwarz<sup>23</sup> noted that contractions were markedly activated under the influence of distending enemas. Walsham and Overend stated that these movements are due to true peristaltic waves, with a rate of from one to two a minute, and that they are abolished by nicotine or curare and probably originate from nodal tissue. Walsham and Overend described smaller rhythmic contractions with waves coming at the rate of about twelve each minute, which they claimed had no directive power but exhibited periodic augmentation and were either purely myogenic or myoneurogenic. These were practically identical to those observed by Isémein and Poinso. Hurst,<sup>67</sup> in 1922, found that the tonus and movements of the colon depend largely on the bulk of its contents, and these varied continuously with the amount of gas and feces present. He also observed that the descending and pelvic portions of the colon were usually empty and consequently in a state of tonic contraction with more or less obliteration of its lumen, whereas the opposite condition was present on the right side. Here the content was fluid or semifluid, the tonus was less and the lumen greater, so that he considered it normal to find a large splashy cecum when the portion of colon felt on the left side gave the impression of a solid cord. From his roentgenologic observations on human subjects, he noted that the colon was quiet most of the time and only changed materially after hours in which a meal was taken.

Hickey<sup>68</sup> found the movements of the colon by the barium sulphate enema so slow and so infrequent that opportunities to observe them were rare, and in most cases, whether the colon is filled by a barium meal or by a barium enema, the examiner can report only the size, shape and relation of the component parts of the large intestine. However, by overdistending the organ with large enemas of opaque material he saw peristalsis begin in the transverse colon and pass along to the splenic flexure, forcing the content onward and distending the upper portion of the descending colon. The content may be interrupted temporarily here but it soon passes on, emptying the lower portion of the descending colon and starting up peristaltic waves in the sigmoid which may result in

66. Bergmann, quoted by Schwarz.<sup>26</sup>

67. Hurst, A. F.: Sins and Sorrows of the Colon, *Brit. M. J.* 1:941 (June 17) 1922.

68. Hickey, P. M.: Peristalsis of the Colon, *Am. J. Roentgenol.* 9:260 (April) 1922.

evacuation. About this time peristalsis starts in the cecum, emptying it rapidly and passing onward to the transverse colon where the procedure again takes place. Flint<sup>69</sup> holds an opinion similar to that of Hickey in that he found the colon quiet most of the time except after meals, and Murray<sup>70</sup> stated that normal peristalsis does not take place until the colon is full. Macleod<sup>71</sup> regards the descending colon as a tube for the transferring of masses from the transverse colon; he claims it is never distended. Rokitsansky, in 1842, stated that this portion of the colon is normally empty. This fits in well with the study of Gleize-Rambal,<sup>72</sup> who observed that there is a line of demarcation between the transverse and descending portions of the colon which makes the distal colon well suited for strong muscular efforts to evacuate it. The descending portion is smaller and rounder and maintains its shape with greater ease than the transverse portion which is large, thin-walled and transparent. Microscopically, the muscularis of the descending portion is thick, and that of the proximal portion is poor in longitudinal fibers. He also found the cellular structure denser and thicker on the transverse portion with correspondingly greater amounts of mucus in this region. His observations were made on cadavers, at laparotomy and roentgenographically. Similarly, Kirkes<sup>73</sup> found that the muscular fibers of the colon become stronger as they progress distally, and are strongest in the rectum where greatest tension is exerted. Schellberg<sup>74</sup> considered the attachment of the colon at the hepatic and splenic flexures as important in the performance of their movements, which, he stated, are deliberate and seldom take place. Mills<sup>75</sup> described three movements of the colon expressed in relation to the colonic rugae, in which Forsell<sup>76</sup>

69. Flint, Ethelbert: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, *Proc. Roy. Soc. Med. (Sect. Proctol.)* **15**:54, 1922.

70. Murray, D. H., in discussion on Beach, W. M.: The Subnormal Function, *J. A. M. A.* **71**:1453 (Nov. 2) 1918.

71. Macleod, J. J. R.: *Physiology and Biochemistry in Modern Medicine*, ed. 5, St. Louis, C. V. Mosby Company, 1926.

72. Gleize-Rambal, L.: *Sur l'individualité anatomique du côlon descendant*, *Compt. rend. Soc. de biol.* **99**:2015, 1928; *L'individualité structurale du côlon descendant*, *ibid.* **100**:368, 1929; *Note sur la disposition du gros intestin de l'embryon humain du 3<sup>e</sup> mois*, *ibid.* **100**:715, 1929.

73. Kirkes, W. S.: *Handbook of Physiology*, ed. 16, New York, William Wood & Company, 1900.

74. Schellberg, O. B.: *Observations on the Physiology of the Human Colon*, *Internat. J. Med. & Surg.* **41**:40 (Jan.) 1928.

75. (a) Mills, A. E.: *Some Effects of Disturbance of Physiology of Movements of Gastro-Intestinal Tube*, *M. J. Australia* **1**:127 (Feb. 7) 1925. (b) Mills, R. W.: *Studies of the Colon: I. Roentgen-ray Evidence of Colonic Secondary Changes*, *Am. J. Roentgenol.* **11**:487 (June) 1924.

76. Forsell, quoted by Mills.<sup>75 b</sup>

agreed. These, he stated, are: (1) the lateral or nonhaustral canalicular, (2) the general polydirectional haustral and (3) the longitudinal haustral compression movements.

Lenz<sup>70</sup> studied the movements of the colon of the cat through a celluloid abdominal window; Katsch and Borchers<sup>77</sup> have described the technic of this method in detail and saw two types of propulsive movements, annular and tubular, which were entirely distinct from those of defecation. Zondek,<sup>78</sup> in 1921, made a similar study of various animals and observed peristaltic movements occurring with considerable regularity in the dog about every thirty seconds; these were markedly stimulated by the taking of food. He also described haustral segmentation by a similar means in the colon of rabbits, and antiperistalsis as the usual finding in the proximal portion of the large intestine in the cat, rat, guinea-pig and other mammals. Plant and Miller,<sup>79</sup> using balloons in the colons of unanesthetized dogs, observed waves similar to those obtained by Templeton and Lawson. The latter investigators used a tandem set of six balloons in the dog's colon, three of which were inserted through a cecostomy opening and three through the rectum, and obtained some excellent records of the character of the movements of the large intestine. With this preparation simultaneous tracings were made of the entire colon. In the proximal portion, activity was distinctly periodic with contractions superimposed on changes in tonus, whereas in the distal portion changes in tonus were less pronounced but otherwise similar. The point at which the change took place was at the splenic flexure. They also found that the entire colon could act as a unit, but that the activity was subject to sudden alterations in the formation of waves going in either direction. In general, their results confirm those of other investigators.

*Mass Movements.*—One of the most interesting and frequently disputed movements of the colon is the so-called mass movement, it was described by Hertz<sup>80</sup> in 1907 and 1908, Hertz, Cook and Schlesinger<sup>81</sup>

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77. Katsch, Gerhardt, and Borchers, Eduard: Beiträge zum Studium der Darmbewegungen. I. Das experimentelle Bauchfenster, Ztschr. f. exper. Path. u. Therap. **12**:225 (Jan. 8) 1913.

78. Zondek, B.: Ueber Dickdarmperistaltik, Beobachtungen am experimentellen Bauchfenster, Arch. f. Verdauungskr. **27**:18, 1920; abstr., J. A. M. A. **76**:346, (Jan. 29) 1932.

79. Plant, O. H., and Miller, G. H.: Effects of Carminative Volatile Oils on the Muscular Activity of the Stomach and Colon, J. Pharmacol. & Exper. Therap. **27**:149 (March) 1926.

80. Hertz, A. F.: The Pathology and Treatment of Chronic Constipation, Proc. Roy. Soc. Med. (Sect. Med.) **1**:119, 1908.

81. Hertz, A. F.; Cook, F., and Schlesinger, E. G.: The Action of Saline Purgatives, Guy's Hosp. Rep. **63**:297, 1909.

in 1909. Holzkecht in 1909, Barclay<sup>82</sup> in 1912 and Kaestle in 1912, and later by many others. Previous to the paper by Holzkecht in 1909, there seems to be no detailed statement concerning the mechanics of the propulsion of the fecal content over considerable areas, and credit should be given him for recognizing and describing these movements in detail. In brief, this movement is as follows: It is the principal normal propulsive movement of the colon taking place three or four times a day, serving to move the contents of the bowel from the antiperistaltic influence of the proximal portion of the colon through to the distal portion. The mechanism, as Holzkecht explains, may possibly be a powerful peristaltic wave, but more likely is associated with a tonic contraction of the circular coat of the part of the colon through which the wave passes. The haustral markings disappear and fecal matter seems to run together in a sausage-like bolus, which has smooth edges and is rounded at the ends. The mass at once begins to move at about twice the rate of peristaltic waves in the stomach, and the rate and distance of this movement are variable, sometimes transporting the fecal content from the cecum to the pelvic colon or rectosigmoid without stopping. When it comes to rest, haustral indentations reappear. Alvarez observed these mass movements often secondary to a rush wave in the small bowel and frequently resulting in a call to defecation. According to Case, they are most often seen before or during defecation. These movements are accompanied by a gurgling sound, due, Kaestle stated, to the accumulation of gases in advance of the moving mass, and expanding the colon ahead, thus facilitating movements over long distances. Diarrheal cramps, Case stated, are often accompanied by mass movements, and Alvarez saw these contractions in patients with a tendency to diarrhea. Kaestle noted these movements in a woman; the entire colon took part, contracting down to the size of a cord, but it was so marked and long continued, as well as accompanied by such severe spasmodic pain, that he concluded it was due to a disorder of innervation of the colon. Hertz,<sup>44</sup> in 1909, and also Welch,<sup>83</sup> in 1925, noted perceptible progress through the colon after meals, but otherwise this was very slow. Barclay,<sup>84</sup> in 1911, 1912 and 1913, studied these movements carefully and blamed defects in mechanism of this type of activity as resulting in stagnation in the rectum and other parts of the colon, and being one of the causes of constipation. In a further study in

82. Barclay, A. E.: Note on the Movements of the Large Intestine, Arch. Roentgen Ray **16**:422 (April) 1912.

83. Welch, P. B.: What Constitutes Constipation: Some Observations on Colon, J. Iowa M. Soc. **15**:18 (Jan.) 1925.

84. Barclay, A. E.: Radiological Studies of the Large Intestine, Brit. J. Surg. **2**:638, 1914-1915. Barclay<sup>82</sup>.

1909 and again in 1913, Hertz,<sup>85</sup> and also Betz, in 1912, corroborated Holzkecht's view and added that the chief stimulus to this movement is entry of food into the stomach, and designated it as the gastrocolic reflex. Holzkecht, incidentally, noted the mass contraction after feeding a second bismuth meal. Hertz<sup>44</sup> further observed that normally the ileocecal sphincter held back the content in the terminal ileum for a considerable time, relaxing principally during meals, at which time the greater part of the content entered the cecum. Peristalsis in the lower part of the ileum became more activated at meal time. Hertz and Newton, in 1913, saw the phenomenon in a patient with partial intestinal obstruction due to carcinoma of the rectosigmoid juncture, and noted that the contents of the colon passed from one end to the other in a second or two, with no signs of either peristalsis or antiperistalsis.

Isémein and Poinso explained the mechanism of the gastrocolic reflex as consisting either of stimulation of the colon by a hormone from the gastric mucosa or of stimulation of the circular muscles of the small intestine down from the stomach and extending to the large bowel. Likewise, Betz, in 1912, considered the stomach and rectum as the principal reflex routes for stimuli to the intestine. Alvarez regarded the gastrocolic reflex as involving the mesenteric nerves.

In 1916, Walsham and Overend reported observations on sporadic mass movements following chiefly either the entrance of food into the empty stomach or evacuation of the bowel, and again in 1922, Hurst corroborated these observations, stating further that after the absorption of water from the contents of the right half of the colon the fecal matter is moved from the cecum to the pelvic colon, where it remains until mass movement carries it farther. They found that during the day the greater part of the cecal, ascending and pelvic portions of the colon are more or less full and the remaining part is empty. In a careful study, Welch and Plant,<sup>86</sup> using balloons placed in the stomach and colons of dogs through fistulas, and in the colons of human subjects, obtained tracings. Their observations showed that the normal muscular activity of the colon is very irregular and great variations in tonus and contractions occur, with the colon never in the state of complete inactivity which Holzkecht found. After feeding the dogs, they obtained a definite increase in tonus of the colon in from half a minute to several minutes, lasting from ten to twenty or up to sixty minutes. Sometimes this reaction would be repeated several times, but more often there was no second effect. By feeding through a fistula in the stomach, such results were not obtained. They therefore claimed that to call this

85. Hertz, A. F.: The Ileo-Caecal Sphincter, *J. Physiol.* **47**:54 (Oct. 17) 1913.

86. Welch, P. B., and Plant, O. H.: A Graphic Study of the Muscular Activity of the Colon, with Special Reference to Its Response to Feeding, *Am. J. M. Sc.* **172**:261 (Aug.) 1926.

reaction a "gastrocolic reflex" was a misnomer and that it is really a "feeding reflex" or "appetite reflex," similar to that of gastric secretion, depending not on distention of the stomach with food but more on psychic stimulation. They further substantiated this opinion by obtaining a typical result with merely the entrance of the attendant who usually fed the dog. They also demonstrated that with an empty bowel the effect was much less or was even absent, as contrasted to that obtained when the bowel was full. Schellberg, in 1928, considered the presence of gas as important in mass movements, and also that chemical activity of the fecal content on the mucosa played a considerable part in this and other types of movements of the colon. Draper and Johnson<sup>87</sup> disagree with former opinions of mass movements and stated that propulsion of the contents of the colon takes place by slow imperceptible segmentation contractions and probably not by so-called "mass movements" which they were never able to see. Hines, Lueth and Ivy,<sup>88</sup> in 1929, put balloons into the rectums and sigmoids of human subjects, through a proctoscope. They found two definite types of curves, one a slow, slight rhythmic elevation with a tonus rhythm and the other steep contractions. Among twenty-one normal students they obtained a steep contraction in five only after meals, and this was concomitant with an urge to defecation. They felt this was probably the gastrocolic reflex of other investigators. Such urge was not present if the subjects were constipated, and steep waves could not be obtained at any time with similar technic. They concluded, therefore, that the threshold for sensation in cases of constipation is raised. They also concluded that the latter type of movement is an involuntary aid to defecation. Movements similar to the mass contraction of Holzknecht were obtained by Ganter and Stattmüller.<sup>89</sup> Using a balloon in the colonic stoma of a patient with chronic ulcerative colitis, they obtained high contractions in groups similar to those obtained by Hines, Lueth and Ivy. Peiper,<sup>90</sup> by putting a double balloon in the distal colon of children, found that usually there was no activity, although if diarrhea was present there was a pendular type of movement.

*Defecation.*—Cannon,<sup>3</sup> in 1902, observed the process of defecation by roentgenographic means and described it as a slow, sweeping move-

87. Draper, J. W., and Johnson, R. K.: *The Pathogenic Colon: Recent Studies*, *Am. J. Surg.* 4:1 (Jan.) 1928.

88. Hines, L. E.; Lueth, H. C., and Ivy, A. C.: *Motility of the Rectum in Normal and Constipated Subjects*, *Arch. Int. Med.* 44:147 (July) 1929.

89. Ganter, G., and Stattmüller, K.: *Studien am menschlichen Darm: III. Ueber die normalen Dickdarmbewegungen des Menschen und ihre Beeinflussung durch Pharmaka*, *Ztschr. f. d. ges. exper. Med.* 42:143, 1924.

90. Peiper, Albrecht: *Bewegungen des Magen-Darmkanals im Säuglingsalter*.  
4. *Der Dickdarm*, *Jahrb. f. Kinderh.* 120:312, 1928.

ment in which the bowel swung around so that the ascending colon lay in the position of the distal half of the transverse portion, and the latter took the position of the descending part. At the same time tonic contractions disappeared and were replaced by strong, broad contractions of the circular muscle, tapering the contents off on each side into two cones. As the intestine swung around, more material was forced into the rectum by constriction, dividing the lumen, which passed slowly downward aided by the abdominal musculature. Usually some material was left behind in the cecum. Hertz<sup>44</sup> described this act as consisting of contractions of the diaphragmatic and abdominal muscles which resulted in a considerable increase in pressure in the abdomen since the glottis was kept closed, aiding in forcing more feces into the rectum. Through the stimulation thus produced in the rectum, involuntary peristalsis starting well back in the colon was initiated. Included in this chain of reflexes was inhibition of the internal sphincter. His impression was that the entire colon took part in the act, but that only the bowel distal to the splenic flexure was evacuated, and in some cases even the rectum was not completely emptied. The content of the right part of the colon moved over to the descending colon to take the place of that which was evacuated. Schwarz's<sup>28</sup> observations were of a similar nature, except that he saw fecal masses go through almost the entire length of the colon and this movement was associated with contractions of that organ. By the introduction of stimulating enemas he demonstrated a similar process, and could by this method obtain evagination and invagination of the haustra. He further demonstrated roentgenologically that prior to, and during, defecation there regularly occurred coarse movements of the large intestine. These occurred typically as cramps and were often associated with diarrhea. Schwarz<sup>23</sup> attributed propagation of intestinal contents to the fine and coarse movements of the large intestine and also to the increased intra-abdominal pressure. In this connection it may be noted that Jonas,<sup>91</sup> in 1912, found in his studies on achylia gastrica that diarrhea was associated with a hypermotility of the entire gastro-intestinal tract and not necessarily of the large bowel alone. Also, he noted that if the propulsion of the contents was abnormally fast in the small intestine, a normal stool could still result, providing there was a delay in the passage through the distal portion of the colon.

There probably is no distinct desire to empty the bowels until feces have actually reached the rectum and produce distention there, as Howell has pointed out, and as Hertz and Newton, in 1913, were able to see roentgenographically. The feces are retained by tonic contraction of the

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91. Jonas, Siegfried: Ueber das Verhältnis zwischen Stuhlbild und Darmmotilität und die wechselnden Stuhlbilder der Hyperacidität und der Achylie, Arch. f. Verdauungskr. 18:769, 1912.



areas in the brain where stimulation affected the tonus of the sphincters. However, it is probable, as Alvarez stated, that the most important centers for the sphincters are in the third and fourth sacral segments of the cord. This was substantiated by Goltz,<sup>95</sup> and also by Goltz and Ewald's<sup>96</sup> observations that immediately after destruction of the lumbar and sacral cord in dogs, the anus was relaxed and gaping. Occasionally there was diarrhea, but this gradually cleared. In time defecation became normal and there was no atrophy of the sphincter, showing that the rectum and sphincters act by virtue of their own intrinsic mechanism, a faculty which Alvarez attributed to the high autonomy of the rectum.

When there is nothing to start the chain of reflexes which brings about defecation, such as loss of sensation in the rectum, it is then that the most severe disturbances are produced. Merzbacher,<sup>97</sup> in 1902, demonstrated this by cutting the sensory roots of the three sacral nerves of the dog. The animals were not aware of anything in the rectum because of the anesthesia produced. The feces became dried out, no attempt was made by the animal to defecate, and it was only when a considerable amount of material collected in the rectum that it was pushed out passively. This is likewise true in human subjects, as noted by Bälint and Benedict,<sup>98</sup> in 1905 and 1906, who studied six cases of lesions of the conus terminalis and found that the patients were generally constipated in spite of relaxation of the anal ring and anesthesia of the mucosa of the rectum. However, they could control the bowel movements fairly well. These observers made no roentgenographic observations of the colon. McIntosh,<sup>99</sup> in 1929, confirmed this in observing a child, aged 6 years, with a lesion of the spinal cord in the lumbosacral area. He found marked stasis of the colon; it took a barium meal twelve days to reach the rectum and longer to be expelled. It took ten days for it to pass from the splenic flexure down so that most of the retardation was in the left portion of the colon. The tonus of the large bowel was apparently good, the haustra appeared normal, and there was no localized atony or dilatation. McIntosh agreed with other observers in that it seemed to him that the trouble was chiefly

95. Goltz, F.: Ueber die Functionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. 8:460, 1874.

96. Goltz, F., and Ewald, J. R.: Der Hund mit verkürzten Rückenmark, Arch. f. d. ges. Physiol. 63:362, 1896.

97. Merzbacher, L.: Die Folgen der Durchschneidung der sensibeln Wurzeln im unteren Lumbalmark, im Sacralmark und in der Cauda equina des Hundes, Arch. f. d. ges. Physiol. 92:585 (Nov. 5) 1902.

98. Bälint, R., and Benedict, H.: Ueber Erkrankungen des Conus terminalis und der Cauda equina, Deutsche Ztschr. f. Nervenhe. 30:1 (Dec. 20) 1905.

99. McIntosh, Harriet C.: Roentgenologic Study of the Colon in a Child with a Spinal Cord Lesion, Am. J. Roentgenol. 22:247 (Sept.) 1929.

internal sphincter until defecation begins, then the sphincter relaxes and masses are forced through the anal canal by the combined efforts of the rectal and abdominal muscles. In other words, it is normally both a voluntary and an involuntary action. The minimal pressure within the rectum found by Hertz<sup>41</sup> to initiate a call to defecation was between 3 and 4 mm. of mercury, and the pressure within the rectum may become from four to eight times that much during the act as a result of the increased intra-abdominal pressure. The latter then caused more material to enter and to distend the rectum, and resulted in still stronger contractions of abdominal and rectal muscles as well as a corresponding relaxation of the internal sphincters. Severe pain may be produced by using extreme distention in the colon, as Fröhlich and Meyer<sup>92</sup> have shown. They attributed this either to spasm of the circular musculature or to irritation of the peritoneal coat. Alvarez noted a tendency sometimes in man to empty the rectum completely by a process of prolapse and eversion of the mucous membrane, and Starling stated that the last section of the rectum is emptied at the close of defecation by forcible contractions of the levator ani and other perineal muscles, contractions which serve to restore the everted mucous membrane. Luciani considered peristaltic activity of the sigmoid and rectum as most essential in the act of defecation, although inhibition of tone of the internal sphincter, contractions of the levator ani and abdominal compression by contractions of the diaphragm and abdominal musculature along with closure of the glottis are important factors.

A spurious desire to move the bowels may be aroused by pressure from external sources on the walls of the rectum, such as from a large calculus of the bladder, prostatic tumor or fetal head in the pelvis. The same effect may be noticed from internal hemorrhoids, tumor of the rectum or an inflammatory disease present in that region.

Defecation may be restrained by several muscles or combinations of muscles, such as the internal sphincter, the external sphincter, the levator ani and the voluntary muscles about the perineum, as Frankl-Hochwart and Fröhlich<sup>93</sup> pointed out.

There are other factors which influence or take part in the act of defecation, namely, centers in the brain and spinal cord. Hatcher and Weiss,<sup>94</sup> in 1923, applied small doses (0.016 mg.) of picrotoxin to an area in the floor of the fourth ventricle close to the vomiting center and produced diarrhea almost immediately, and Luciani, in 1913, found

92. Fröhlich, A., and Meyer, H. H.: Die sensible Innervation von Darm und Harnblase, *Wien. klin. Wchnschr.* **25**:29 (Jan. 4) 1912.

93. Frankl-Hochwart, L., and Fröhlich, Alfred: Ueber Tonus und Innervation der Sphinkteren des Anus, *Arch. f. d. ges. Physiol.* **81**:420 (Aug. 11) 1900.

94. Hatcher, R. A., and Weiss, Soma: Studies on Vomiting, *J. Pharmacol. & Exper. Therap.* **22**:139 (Oct.) 1923.

sensory impairment of the rectum and that there was no excitant to initiate mass movements. Also, there was no sudden entry of a large amount of material into the rectum as there is when mass contractions take place. Peculiarly enough, it is the experience of neurologists that there is no definite relationship between the level of the situation of a tumor of the spinal cord and the degree of disturbance of sphincter function.

The fact that most people perform the act of defecation in the morning soon after breakfast is generally ascribed to several factors. During the night the contents of the colon are gradually moved from the proximal to the pelvic and descending portions, and after being comparatively quiet the large bowel is stimulated to activity by the muscular exercise in moving about and by reflex contractions from putting food into the empty stomach. The chain of reflexes thus set up results in a call to defecation.

*Valves of the Rectum.*—The function of the valves of the rectum has been studied by various investigators. Bodenhamer,<sup>100</sup> however, denies their existence as definite valves, claiming them to be merely semilunar ridges of mucous membrane. Pennington<sup>101</sup> described them in detail and stated that they have definite functions, according to his experimental studies on both living and dead subjects. He found that the valves function to prevent feces from crowding down on the anus, that they equalize the pressure of the feces that accumulate in the rectum from time to time and that they facilitate defecation by giving a spiral motion to the content of the bowel. In support of his views, he cited the fact that man is the only animal possessing them and he is the only animal that defecates regularly. Irritants and foreign bodies cause them to become erect and present as a sort of ledge across the bowel, and in some cases they are directed upward, forming distinct cups or pockets, as demonstrated in plaster casts taken of them. In certain subjects they are enlarged, sometimes so much that they may interfere with normal defecation.

*Other Movements of the Colon.*—A fifth variety of movement takes place in the colon, which is described ordinarily as a pendulum or large swinging type of motion, and has been observed chiefly during roentgenologic studies. These movements seem to be concerned especially with the aid of absorption and take place in the transverse colon. This portion of the colon assumes a totally different position, first being in a high and in a few minutes in a lower part of the abdomen.

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100. Bodenhamer, W.: Are There Veritable Valves in the Rectum? New York M. J. **71**:1026 (June 30) 1900.

101. Pennington, J. R.: New Points in the Anatomy, Histology, and Pathology of the Rectum and Colon, Chicago M. Rec. **19**:392, 1900.

This motion was described by Walsham and Overend, in 1916, by Rieder,<sup>102</sup> and by Currie and Henderson,<sup>103</sup> in 1926, who also noted gentle swaying movements in direct observations on the colon of the guinea-pig, which they thought were produced mainly by the longitudinal muscles. In addition to the type of movement studied by the aid of the roentgen rays, by abdominal windows and by direct observation, valuable contributions have been made by the observation of strips of bowel excised from the large intestine.

Alvarez commented on the sluggishness of the colon and exhibited many tracings to show the contractions of excised bits of its musculature, which reveal a very slow rate with pronounced tonus waves. From five different segments of the cecum there was little difference, the beats possessing little rhythmicity, as compared with that of the small bowel. Kolda,<sup>104</sup> in 1926, made similar observations on the large intestine of the cat and obtained six contractions, at the rate of six in five minutes, and these were of a similar nature to Alvarez's results. From the studies of Alvarez and Starkweather, there appears to be a downward metabolic gradient (determined by the catalase content) from the tip to the base of the cecum of rabbits and guinea-pigs. From the base the gradient is upward to the colon. They bring out a physiologic reason for this difference in that the cecum is a food reservoir which, in order to retain its contents, contracts seldom and is not influenced by happenings in the other parts of the gastro-intestinal tract. Cannon,<sup>15</sup> in 1911, showed that mechanical extension was the most efficient stimulus for exciting activity in the colon, just as it is for other types of smooth muscle such as that of the small bowel, ureter and bladder. Magnus,<sup>105</sup> in 1904, seems to have been first to record the longitudinal movements of short length strips of bowel, which has been called the Magnus method. Currie and Henderson used strips from the first part of the ascending colon of the guinea-pig and found small, rhythmic movements with a rate of about thirty-eight each minute, and at times larger contractions which they thought were the result of summation of the smaller ones. In the transverse colon, the strips beat rather irregularly with long, slow tonus waves, and in the sigmoid portions they obtained high tonus waves, but these were less frequent than those of the transverse segment.

102. Rieder, H.: Die physiologische Dickdarmbewegung beim Menschen, Fortschr. a. d. Geb. d. Röntgenstrahlen **18**:85, 1912.

103. Currie, G. C., and Henderson, V. E.: A Study of the Movements of the Large Intestine of the Guinea Pig, Am. J. Physiol. **78**:287 (Oct.) 1926.

104. Kolda, J.: Contribution à l'étude des mouvements de l'intestin isolé, Compt. rend. Soc. de biol. **95**:210, 1926.

105. Magnus, R.: Versuche am überlebenden Dünndarm von Säugethieren: II. Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung, Arch. f. d. ges. Physiol. **102**: 349 (April 9) 1904.

Gross,<sup>106</sup> Flint,<sup>68</sup> Keith<sup>107</sup> and others noted the effect of a diet deficient in vitamins on the movements of the strips of colon of rats. Ordinarily, they beat with a rhythm of from two to three contractions each minute, but after deprivation of vitamin B, contractions were not elicited, and the result of this in vivo, they showed, was definite stasis in the intestinal tract. The latter was evidenced by dilatation of the ascending colon, by the filling of the descending colon with feces and by the presence of an increased number of ileocecal glands.

*Reflexes Involving the Colonic Movements.*—Many factors operate to aid in unifying and rendering the functions of the large intestine purposeful, and disturbance of or interference with any of these factors may lead to abnormal or ectopic movements. Just as with many other portions of the body, the colon is subject to reflexes, and although not many of these can be readily explained, yet a few have been studied thoroughly. Probably the most important of these is the gastrocolic or feeding reflex which has been described. Inflammatory lesions in the ileocecal region, such as appendicitis, may produce all grades of back pressure<sup>18</sup> up to the vomiting of large amounts of fluids and likewise intestinal injury, such as cutting and handling of the bowel, will delay the emptying time of the stomach.<sup>11</sup> This no doubt is a protective mechanism for the purpose of holding back food until the bowel becomes healed. Many investigators have shown that distention of the colon delays emptying of the stomach. White<sup>108</sup> produced intense irritation of the cecum of cats with mustard and olive oil, and also with croton oil, and obtained definite delay in the emptying of the stomach and even in vomiting. However, with a moderate or even a marked degree of irritation there was usually no effect. Smith and Miller<sup>109</sup> obtained increases in tonus as well as in peristaltic activity of the stomach and pylorus by irritation of the cecum or appendix with croton oil. Percy and Van Lier<sup>110</sup> distended the colons of dogs and found that during vigorous hunger contractions of the stomach the contractions ceased and complete inhibition took place. If the distention was continued, it

106. Gross, Louis: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) 15:71, 1922.

107. Keith, Arthur: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) 15:60, 1922.

108. White, F. W.: The Effect of Disease of the Lower Bowel on the Rate of Emptying the Stomach, Med. & Surg. 2:618 (June-July) 1918.

109. Smith, F. M., and Miller, G. H.: The Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach, Arch. Int. Med. 46:988 (Dec.) 1930.

110. Percy, J. F., and Van Lier, E. J.: Reflexes from the Colon, Tr. Am. Gastro-Enterol. A., 1925, p. 135.

caused nausea, salivation and vomiting. Smith, Paul and Fowler<sup>111</sup> noted increases in activity of the stomach and especially of the pylorus when they injected air into the large intestine or massaged the cecum of patients with an irritable colon. They thus showed the presence of a definite reflex involving the colon and stomach. King<sup>112</sup> has shown that stimulation of the colon caused inhibition of the motor, secretory and absorptive functions of the small bowel. Percy and Van Lierie also obtained cardiovascular respiratory reflexes from distention of the colon consisting of what appeared to be auricular extrasystoles and auricular flutter. Blood pressure also rose from 30 to 60 mm. of mercury and in some cases in man, from 20 to 25 mm. of mercury, remaining elevated as long as nine hours, and the subjects complained of flushed skin and free perspiration. In dogs they obtained an increased volume of the kidney and increased tonicity of the bladder.

More recently, Monroe and Emery,<sup>113</sup> after determining normal values, studied the emptying time of the stomach following irritation of the colon by turpentine, and their results indicated that the emptying time of the stomach was not especially influenced by irritation of the colon. However, there was no involvement of the peritoneum in their experiments, so it is possible that the difference in results of other investigators may have been due to this.

In a different type of experiments, in which the conditions were reversed, Surmont, Dubus and Tiberghien<sup>64</sup> applied stimuli to the pre-pyloric and duodenal regions of dogs and cats and noted the effect on the colon. In some cases no reaction whatever could be elicited on the large intestine, but in many of them contraction waves were recorded in the colon within one minute of the time of stimulation in the upper part of the intestinal tract. This, they explained, was due to a reflex and not to a peristaltic wave passing downward, because there was not enough time for this to take place. They thought it might be related to the gastrocolic reflex. Lyman, in 1913, in confirming Cannon's<sup>11</sup> view that the proximal part of the colon becomes quiet and relaxed as food nears the ileocecal valve, observed cats anesthetized with ethyl carbamate and then injected a mixture of starch and paste into the ileum near the valve. He noted that the colon a moment before was in tonic contraction, but as the material passed through the valve, the large intestine became motionless and relaxed, and as soon as the process was finished waves reappeared in the colon. He concluded that the mecha-

111. Smith, F. M.; Paul, W. D., and Fowler, W. M.: Mechanism of Epigastric Distress Associated with an Irritable Colon and Chronic Appendicitis, *Arch. Int. Med.* **47**:316 (Feb.) 1931.

112. King, C. E.: Studies on Intestinal Inhibitory Reflexes, *Am. J. Physiol.* **70**:183 (Sept.) 1924.

113. Monroe, R. T., and Emery, E. S., Jr.: The Effect of Irritation of the Colon on the Emptying Time of the Stomach, *Am. J. M. Sc.* **177**:389 (March) 1929.

nism was a local one because he could obtain it in the absence of nervous connections to the spinal cord, and that it was an example of reciprocal innervation of opposed muscles.

Drury, Florey and Florey,<sup>114</sup> in 1929, exteriorized a small segment of colon and demonstrated that when the dog was frightened and when local stimulation was applied this patch would turn pale, even when it was denervated, but it would not necessarily do so during mass movements. Even with movements in the portion, pallor was not observed. They do not explain the nature of the phenomena. White increased the tonus of the colon and, in this way, stimulated peristalsis by vigorous massage of the contents of the large intestine under the fluoroscopic screen. Incidentally, he was unable to move fecal matter by such massage. The value of exercise in the correction of constipation no doubt can be explained on the basis of the massaging action of the abdominal musculature on the intestinal tract, as noted by Soper.<sup>115</sup> The effect of exercise on the behavior of the colon has been reviewed in detail and studied extensively in some researches of their own by DeYoung, Rice and Steinhaus.<sup>116</sup> By inserting single balloons into a cecostomy opening in the colon of the dog, with the animal on a treadmill, they obtained rises in the motility and tonus of this organ. This increased activity was not coexistent with the period of exercise but started from one to three minutes later and receded in a few minutes, regardless of the duration of the exercise. They attempted to trace the origin and nature of this rise from exercise by sectioning the colon near the ileocecal valve in some instances, and in others near the anus. With the balloon between the two "cuts," no "exercise" response could be elicited, but above and below the two cuts, typical results were obtained. From this they deducted that there is a second parasympathetic inflow to the colon, probably vagal, coming in at the proximal end of the large intestine, and movements are stimulated by an unusual outflow of impulses during exercise. (The sympathetic nerves were intact in these experiments.) DeYoung, Rice and Steinhaus consider these rises in tonus and motility with exercise as similar in nature to the "mass movements" seen in man. Other factors which stimulate movements of the colon are the presence of formed fecal material in the rectosigmoid, gradual intermittent dilatation of the anal canal, the presence of food in the stomach and the act of defecation.

114. Drury, A. N.; Florey, H., and Florey, M. E.: The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, *J. Physiol.* **68**:173 (Oct. 23) 1929.

115. Soper, H. W.: Studies of the Colon: II. The Restoration of Colonic Function, *Am. J. Roentgenol.* **11**:503 (June) 1924.

116. DeYoung, V. R.; Rice, H. A., and Steinhaus, A. H.: Studies in the Physiology of Exercise: VII. The Modification of Colonic Motility Induced by Exercise and Some Indications for a Nervous Mechanism, *Am. J. Physiol.* **99**:52 (Dec.) 1931.

*Motor Tests of Function.*—At present there are no known tests by which the estimation of the function of the colon may be determined with any degree of accuracy. It is true that by roentgenoscopic and other means the time required to empty the contents of the colon has been observed repeatedly, and some idea of the normal function of the large intestine can be obtained by these methods; yet individual variations are so great and so many factors, both extrinsic and intrinsic, exert their influence that these methods do not always seem to be reliable. Hertz,<sup>117</sup> in his observations, felt that the time required for a meal to be evacuated from the gastro-intestinal tract was about from thirty-three to forty-eight hours. He also found that the meal should reach the splenic flexure in about twenty-four hours, and this, in general, is the opinion of most roentgenologists. Kretschmer<sup>117</sup> believed the type of food itself to be a potent factor in the rate of passage through the intestinal tract; in general, coarse food progressed farther. The difference, he thought, was mostly in the small intestine and upper portion of the colon. Likewise, Burnett<sup>118</sup> stated that a badly proportioned dietary regimen was responsible for many disturbances in intestinal function, and the literature is replete with suggestions of this type. Elliott and Barclay-Smith, Schwarz, Carter,<sup>119</sup> Burnett and others have shown that there is a mixing of colonic contents, mostly in the right colon,<sup>18</sup> so that some of the fecal material may stay in the bowel as long as from three to five days, whereas some is voided the same day it is taken. This has been determined especially by the use of various colored beads, and Alvarez has shown that it may often be longer than this before a meal completely traverses the intestinal tract. By giving different colored small glass beads on three successive days, he found that most of his normal subjects passed only 75 per cent of the beads in about four days and after this it often was weeks before all were passed. After catharsis, the rate of passage was greatly increased and, following that, stool was not passed for a day or two, again emphasizing Alvarez's contention that after thorough defecation bowel movement should not be expected for a time because the gastro-intestinal tract is empty, rather than because of any astringent or constipating action by the drug. Naturally, the rates of emptying of the colon vary considerably; subjects with fast rates usually have soft, frothy and voluminous stools, possibly due to faulty digestion and absorption, and it may be that those with slower rates with well formed small stools show better digestion.

117. Kretschmer, Julian: Röntgenologischer Nachweis diätetischer Beeinflussung der Darmperistaltik, München. med. Wchnschr. **59**:2334 (Oct. 22) 1912.

118. Burnett, F. L.: Faulty Food Factors and Atonic Constipation, J. A. M. A. **83**:996 (Sept. 27) 1924.

119. Carter, L. J.: Fluoroscopic Study of the Large Bowel by the Opaque Enema: Analysis of Eight Hundred Examinations, J. Roentgenol. **2**:355, 1919; Further Report on the Study of the Colon by the Opaque Enema: Summary of One Thousand Examinations, Canad. M. A. J. **10**: 1112 (Dec.) 1920.



*Function of the Appendices Epiploicae.*—One of the characteristic findings by which the large intestine may be distinguished from the small intestine is the presence of the appendices epiploicae. They occur as small pouches of peritoneum in two rows, their line of origin being quite close to the anterior and posterior inferior longitudinal muscle bands, and extend from the cecum to the rectosigmoid juncture. No definite evidence of their true function is available, although many speculations have been made. W. J. Mayo<sup>120</sup> thought that they were capable of a wiping motion similar to the swaying movement of the small bowel, which aided in the defensive forces of the abdomen. Robinson<sup>121</sup> was of the opinion that they were concerned with movements of fluids in the colon, thus aiding absorption, but Harrigan<sup>122</sup> denied this, stating that their structure was simple and that they presented no evidence of a specialized function. It is Rankin's<sup>123</sup> belief that there is no doubt as to their being a part of the defensive mechanism, whether they move or not, because they so often are found sealed to a pathologic process, such as gangrenous appendicitis or diverticulitis. That these epiploic tags may get into mischief is evident from a series of observations by Hunt,<sup>124</sup> who described torsion of them with serious results.

#### ABSORPTIVE AND EXCRETORY FUNCTIONS OF THE COLON

Although it is true that disintegration, digestion and absorption of various foods take place in different parts of the intestine, according to the nature of the aliment, yet there is divergence of opinion regarding the types of material and the mechanism by which absorption takes place in the colon. The anatomy of the colon has been widely studied with reference to its physiology. Starling, in 1926, pointed out that great differences exist in the structure of the colon in different animals, differences which depend not on the zoologic position of the animal but on the nature of its food. The colon of the carnivora is short and narrow with little if any cecum, and it has a relatively unimportant function to discharge in digestion and absorption. Proteins of meat are practically entirely absorbed by the time food reaches the ileocecal valve and the same applies to fats, so that only a small amount of these

120. Mayo, W. J.: *The Principles Underlying the Surgery of the Stomach and Associated Viscera*, Am. J. M. Sc. **133**:1 (Jan.) 1907.

121. Robinson, B. F.: *The Transverse Colon and Its Meso-Colon in 140 Autopsies*, M. Rev. **32**:348, 1895.

122. Harrigan, A. H.: *Torsion and Inflammation of the Appendices Epiploicae*, Ann. Surg. **66**:467 (Oct.) 1917.

123. Rankin, F. W.: *Surgery of the Colon*, New York, D. Appleton and Company, 1926.

124. Hunt, V. C.: *Torsion of the Appendices Epiploicae*, Ann. Surg. **69**:31 (Jan.) 1919.

absorbs. The chief function of the colon of carnivora is that of excretion. The colon of the herbivora is well developed, with sacculated walls, and the cecum is very large. This is necessary because their nutritious matter is enclosed in cells surrounded by cellulose walls, and these must be disintegrated so that absorption can take place, which is accomplished either by bacteria or by ferments in the vegetable cells themselves. In the horse, it seems there is a digestive fluid from the cecum which acts on foodstuffs, either *in vitro* or *in vivo*. In the cecum, under the action of many bacteria, cellulose is dissolved and cells are opened up to allow the contents to escape.

The colon of man is a compromise between the herbivorous and the carnivorous type. Draper<sup>125</sup> claimed that, with reference to the colon, human beings are dogs at birth because of the poorly developed right half of the colon; he further stated that the left half of the colon is of extreme age, of constant and important function and of fixed morphology, compared to the right half. He looks on the persistence of the right segment of the colon of man as the dominance of the experimental lengthening by the herbivora, and considers it ill adapted to man's needs. In support of this he studied the gross form of a number of normal colons and found many variations in size, position and appearance of the right side of the large bowel, as contrasted with the absence of variation on the left side. Even racially there are differences in the length of the colon, as Miloslavich<sup>126</sup> has shown, which depend on changes in environment, food, mode of living and climatic and social conditions. As far back as 1835, Schultz,<sup>127</sup> and in 1849, Brückner,<sup>128</sup> commented on the storage capacity of the cecum and its possible function in digestion, and Keith,<sup>129</sup> W. J. Mayo and others have brought out the fact that the large intestine really begins near the splenic flexure, the right portion, especially the cecum, being more nearly like a second stomach. The right half of the colon simulates that portion of the small bowel with which it derives a common origin. Draper<sup>125</sup> claimed that absorption of water is the earliest known function of the right half of the colon. He also pointed out that the stomach and colon have a common function, storage and churning. In the stomach this serves to blend the water with the

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125. Draper, J. W.: Developmental Reconstruction of the Colon: Animal Researches and Clinical Report of Twenty-Nine Human Cases, *Ann. Surg.* **67**:567 (May) 1918.

126. Miloslavich, E. L.: Racial Studies on the Large Intestine, *Am. J. Phys. Anthropol.* **8**:11, 1925.

127. Schultz, C. H.: Observations and Experiments upon the Functions of the Cecum, *Edinburgh M. & S. J.* **44**:408, 1835; *London M. & S. J.* **8**:427, 1836.

128. Brückner, Carl: Die Function des menschlichen Dickdarms mit Hinblick auf die der Wirbelthiere, Rostock, Adler's Erben, 1849.

129. Keith, Arthur: The Functional Nature of the Caecum and Appendix, *Brit. M. J.* **2**:1599 (Dec. 7) 1912.

ingesta and in the colon to remove it. Neither stomach nor colon aids materially in digestion and each can be dispensed with. Many observers have emphasized the water-absorbing function of the colon, stating that this takes place in the cecum between the ileocecal apparatus and the cecocolic sphincter, a physiologic muscular contracture near the hepatic flexure, further aided by the high attachment of the splenic angle so that fluids all tend to gravitate toward the right portion. If fluids went beyond this point, they would interfere with the storage function of the colon. W. J. Mayo summarized this by saying, "Man eats with his jejunum and ileum, and drinks with his cecum. He prepares his food with organs originating from the foregut and absorbs his nutrition from those derived from the midgut." In the small bowel, water is absorbed in large quantities but its loss is made good by diffusion or secretion of fluid in the intestine, since contents of the bowel at the ileocecal valve are quite as fluid as at the pylorus. In the colon, absorption of water is not compensated by a secretion, according to Howell. Hay<sup>130</sup> stated that absorption in the colon is slower than in the small bowel because of the very nature of the mucosa of the two portions, and also because of the mucus secreted in the large intestine which tends to inhibit absorption.

Regarding absorption of other substances, such as drugs, there is more question. Goldschmidt and Dayton,<sup>131</sup> and Goldschmidt and Binger,<sup>132</sup> using various salts, made extensive studies on the mechanism of absorption from the colon. Using dogs, anesthetized with ether or paraldehyde, they ligated the lower part of the ileum, placed a tube in the cecum and washed through to the anus. They found that distilled water was readily absorbed and that it did not injure the mucosa. They also noted that the colon did not have a one-sided permeability, because sodium chloride passed in or out of the colon, depending on the usual

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130. Hay, M.: The Action of Saline Cathartics, *J. Anat. & Physiol.* **16**:243, 391 and 568, 1881-1882; **17**:62, 222 and 405, 1883; On the Use of Concentrated Solutions of Saline Cathartics in Dropsy, *Lancet* **1**:678 (April 21) 1883.

131. Goldschmidt, Samuel, and Dayton, A. B.: Studies in the Mechanism of Absorption from the Intestine: I. The Colon; A Contribution to the One-Sided Permeability of the Intestinal Wall to Chlorides, *Am. J. Physiol.* **48**:419 (May) 1919; II. The Colon; On the Passage of Fluid in Two Directions Through the Intestinal Wall, *ibid.* **48**:433 (May) 1919; III. The Colon; The Osmotic Pressure Equilibrium Between the Intestinal Contents and the Blood, *ibid.* **48**:440 (May) 1919; IV. The Colon; The Behavior of Sodium and Magnesium Sulphate Solutions, *ibid.* **48**:450 (May) 1919; V. The Colon; The Effect of Sodium Sulphate upon the Absorption of Sodium Chloride when the Salts are Introduced Simultaneously into the Intestine, *ibid.* **48**:459 (May) 1919.

132. Goldschmidt, Samuel and Binger, Carl: Studies in the Mechanism of Absorption from the Intestine: VI. The Colon; The Influence of Calcium Salts upon the Absorption of Sodium Chloride in the Intestine, *Am. J. Physiol.* **48**:473 (May) 1919.

law of osmosis and the level of sodium chloride in the blood. This differed somewhat from Diena's<sup>133</sup> point of view, who maintained that the quantity of such substances passing into the intestines is not related to the osmotic pressure of the liquid introduced. Goldschmidt and Dayton and Goldschmidt and Binger also found that the colon behaves toward a solution of sodium sulphate like a semipermeable membrane, but with magnesium sulphate there was almost no absorption into the blood stream, and the failure of absorption of this substance they regard as of significance in catharsis.

The question of absorption of dextrose from the colon has been dealt with extensively by McNealy and Willems.<sup>134</sup> They reviewed the literature carefully, and their experimental work added valuable knowledge to this subject. With fasting dogs under hypnosis by barbital, they isolated the colon by ligatures at the ileocecum and rectum, and likewise a segment of the lower part of the ileum, about 50 per cent longer, to give about the same absorbing surfaces. They found marked constancy in the absorbing action of the colon, but much variation in that of the ileum; this was checked by determination of blood sugar, taken not from the peripheral blood as it was by former investigators, but from the vessels draining the loop of bowel in which the dextrose had been placed. They found no rise in blood sugar in the blood taken from the loop of colon, but a marked rise in that taken from the ileum. With tap water, they found they could recover 78.6 per cent from the loop of ileum and 57.3 per cent from the loop of colon in an hour, and with physiologic solution of sodium chloride, 62.6 and 52 per cent, respectively, was recovered. McNealy and Willems' conclusions were that there was no appreciable absorption of 5 per cent dextrose from the colon, whereas there was considerable absorption from the ileum. Tap water and physiologic solution of sodium chloride were absorbed rapidly by both ileum and colon. The fate of a dextrose enema, according to them, is as follows: It may stay in situ indefinitely; it may be expelled; its character may be changed by bacterial or other action, absorption may take place, or it may pass into the small bowel. The latter is most likely, according to them, and the success of this type of enema is due to such a process, with consequent absorption in the ileum. In some further studies the same investigators found that the presence of 0.45 per cent sodium chloride in a 2.5 per cent solution of dextrose (a physiologic solution of sodium chloride) favored absorption of the dextrose to a certain degree. With the use of sodium bicarbonate and

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133. Diena, G.: *Studio sperimentale sull' assorbimento da parte dell' intestino*, Arch. per le sc. med. **35**:62, 1911.

134. McNealy, R. W., and Willems, J. D.: *The Absorption of Glucose from the Colon: A Preliminary Study of the Glucose Enema*, Surg., Gynec. & Obst. **49**:794 (Dec.) 1929.

alcohol in a similar manner, they noted no influence on absorption of dextrose. There seems to be no doubt that fluids introduced by rectum are carried as far as the cecum. Whether this is by a reversal of peristalsis or by more mechanical pressure is debatable. Starling, in a study of a patient with a cecal fistula, calculated that 500 cc. of water passes the ileocecal valve in twenty-four hours, and about 400 cc. of this is absorbed, so he feels that the colon of man is of little significance as an organ of absorption.

A number of drugs have been studied from the standpoint of their absorption when given rectally. Hatcher and Wilbert,<sup>135</sup> Menninger and Heim,<sup>136</sup> Lesne, Hoskins,<sup>137</sup> Muirhead, and Barbour and Rappaport found epinephrine to be absorbed from the colon and to give the usual physiologic effect. However, Menninger and Heim found that giving the drug this way is unreliable, producing little if any effect in about half of the cases, but that whatever effect there is persists longer, hence it should be of advantage when long effect and repeated doses are required, as in Addison's disease. Levy gave digitalis rectally and found it taken into venous circulation chiefly by way of the mesenteric and portal systems. By a similar method, he gave sodium iodide, and by roentgenographic methods found it to be absorbed from the lower portion of the sigmoid; with bromides, a similar result occurred. It is commonly known that ether and other anesthetic agents are readily absorbable by rectum and produce narcosis.

Urine, without doubt, can be absorbed from the colon, and in birds and certain lower mammals this is probably at times a normal condition, because of the presence of the cloaca which acts as a common receptacle for ejection of both urine and feces. Baird, Scott and Spencer<sup>138</sup> showed that the entire output of urine cannot be drained into the upper part of the intestinal tract of a dog, as its absorption gives toxic symptoms that cause death in from seven to twelve days. Likewise, Cecil and Cummings,<sup>139</sup> after studying a case in which implantation of the ureters was made low in the colon, felt that prolonged absorption of these products occasionally produced a picture resembling chronic nephritis. However, at present, surgeons do not hesitate to

135. Hatcher, R. A., and Wilbert, M. I.: *Pharmacology of Useful Drugs*, Chicago, American Medical Association, 1915.

136. Menninger, W. C., and Heim, H. S.: *The Rectal Administration of Epinephrin*, *Am. J. M. Sc.* **172**:425 (Sept.) 1926.

137. Hoskins, R. G.: *The Sthenic Effect of Epinephrin on Intestine*, *Am. J. Physiol.* **29**:363 (Jan.) 1912.

138. Baird, J. S.; Scott, R. L., and Spencer, R. D.: *Studies on the Transplantation of the Ureters into the Intestines*, *Surg., Gynec. & Obst.* **24**:482 (April) 1917.

139. Cecil, A. B., and Cummings, R. S.: *The Remote Effects of Absorption of Urine from the Colon: A Case of Traumatic Unilateral Uretero-Intestinal Anastomosis*, *J. Urol.* **2**:469 (Dec.) 1918.

implant ureters into the colon, and they regard any dire results from absorption as unlikely.

Absorption of organic substances in the colon takes place to a much less marked degree than that of inorganic substances and is of considerable significance from the standpoint of the value of nutritional enemas as well as in the mechanism of digestion and absorption.

In spite of all the experiments made during the last few years, authors do not agree regarding digestion and absorption of nutritive matter by the colon. It occurs, of course, to a much larger extent in the ileum, as Reid<sup>140</sup> has shown, but studies on the large intestine are not so conclusive. Maestrini made colonic stomas at different levels in the colon of the rabbit and found that the total nitrogen occurred in largest amount in the first portion of the colon and diminished toward the middle of the transverse portion, and from that point to the rectum remained more or less constant. The maximal amount of soluble nitrogen was found in the ascending colon, and fats showed considerable diminution as far as the transverse colon, so that Maestrini claimed that in the rabbit nitrogenous compounds and fats at least are absorbed in the proximal portion of the colon. Reach<sup>141</sup> found absorption of gelatin was much greater from the large intestine when physiologic solution of sodium chloride was added, and Bernheim<sup>142</sup> commented on the apparent value of the nutritive enema by citing cases in which nourishment was given exclusively for as long as ten months by rectum. Eberhard<sup>143</sup> stated that 300 cc. of milk and two eggs could be absorbed by rectum in from one to two hours, and Mutch and Ryffel<sup>144</sup> found that 88 per cent of the nitrogen of peptonized milk could be utilized when given by rectum. The latter authors advised against the procedure, stating that toxic materials could be produced and absorbed in this manner, and recommended that only dextrose or saline solutions be given this way. Scheel<sup>145</sup> noted that milk and eggs irritated the rectum and were not absorbed, so came to conclusions similar to those of Mutch and Ryffel. Begtrup<sup>146</sup> tried meat and milk

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140. Reid, E. W.: On Intestinal Absorption; Especially on the Absorption of Serum, Peptone, and Glucose, *Phil. Tr., London*, s.B **192**:211, 1900.

141. Reach, Felix: Ueber Resorption von Kohlehydraten von der Schleimhaut des Rectums, *Arch. f. exper. Path. u. Pharmakol.* **47**:231 (March 11) 1902.

142. Bernheim, Albert: Movements of Intestines, *J. A. M. A.* **36**:429 (Feb. 16) 1901.

143. Eberhard, H. M.: Nutrient Feeding per Rectum by the Drop Method, *Am. J. Gastro-Enterol.* **2**:5, 1912.

144. Mutch, N., and Ryffel, J. H.: The Metabolic Utility of Rectal Feeding, *Brit. M. J.* **1**:111 (Jan. 18) 1913.

145. Scheel, V., and Begtrup, E.: Nutrient Enemas, *Ugesk. f. læger* **77**:520 (April 1) 1915; abstr., *J. A. M. A.* **64**:1804 (May 22) 1915.

146. Begtrup, E.: Feeding by Way of the Rectum, *Arch. f. Verdauungskr.* **21**:400 (Nov.) 1915; abstr., *J. A. M. A.* **66**:1062 (April 1) 1916.

amino-acids, along with sugar solutions, and stated there was a definite increase in elimination of nitrogen, so that no doubt some nitrogen was absorbed. In general, Cornwall<sup>147</sup> obtained similar results and recommended nutrient enemas of amino-acids with dextrose and other fluids to maintain nitrogen balance in cases in which food cannot be given by mouth.

Carnot and Bondouy<sup>148</sup> studied the content of the colon of a man through a cecostomy opening and found that carbohydrates pass rapidly into the cecum in which, for the most part, they are absorbed. The presence of starch in the cecum was noted from three to six hours after ingestion, and this also was soon absorbed. Egg albumin was found at the cecum in the form of albumin and albumose, but this gradually disappeared and albumin, albumose or peptone was not seen in the stool, indicating that some absorption took place.

In this connection, Howell showed that the splitting of the protein molecule is completed by the process of putrefaction, and the list of end-products is long: peptones, proteoses, ammonia and amino-acids; also indol, skatol, phenol, phenylpropionic acid, phenylacetic acid, fatty acids, carbon dioxide, hydrogen sulphide and marsh gas. Phenol, indol and skatol, he stated, are absorbed and excreted in the urine. However, from Carnot's and Bondouy's<sup>148</sup> study on the absorption of fats in the colon, they could come to no definite conclusions. They found neither biliary pigment nor bile salts at the cecum, although urobilin was present. Áldor<sup>149</sup> found that fats were slower to absorb when given by rectum than either carbohydrates or albumins. However, it seems that the main difficulty in dealing with nutrient enemas, according to Goodman,<sup>150</sup> is that a nitrogen balance cannot be maintained by their use alone, due to inability of the colon to absorb or to render absorbable nitrogen-containing compounds in the enemas. From Howell's observation it seems that considerable digestion may take place in the colon, as dogs with from 80 to 83 per cent of the small bowel removed seemed to get along quite well unless excess roughage or fat was given in their diet. Starling, however, stated that little if any absorption of egg albumin or caseinogen solution takes place by rectum. In his experiments, a small amount disappeared in a considerable time, and he considered this due to bacterial action. He concluded that feeding by

147. Cornwall, E. E.: A Plan of Rectal Feeding, *J. A. M. A.* **70**:1451 (May 18) 1918.

148. Carnot, P., and Bondouy, H.: État de la digestion au niveau du cæcum, *Compt. rend. Soc. de biol.* **81**:487, 1918; État de la digestion au niveau du coecum, *Arch. d. mal. de l'app. digestif* **10**:123, 1919.

149. Áldor, Louis: Untersuchungen über die Verdauungs- und Aufsaugungsfähigkeit des Dickdarms, *Zentralbl. f. inn. Med.* **19**:161 (Feb. 19) 1898.

150. Goodman, E. H.: Diseases of the Digestive Tract and Allied Organs, the Liver, Pancreas, and Peritoneum, *Progrès méd.* **4**:17, 1915.

nutrient enemas is of no value and should be limited to saline solutions, water and dextrose.

*Excretion.*—That the physiology of the colon includes more than that of absorption and expulsion is evident from the numerous studies which have been made on its function as an excretory organ. Voit,<sup>151</sup> as far back as 1860, noted that in fasting dogs the amount of fecal material often exceeded the amount of food eaten, and since then many authors have noted that the excretion products of the intestinal mucosa take part in the formation of the fecal material. Peola<sup>152</sup> stated that in many instances the greatest quantity of feces is not made up of alimentary products, but of those of excretion from the intestine, and especially from the large bowel, although Voit stated that most of this excretion is confined to the small intestine. Voit further contended that almost all of the nitrogen content of the feces comes from intestinal secretions. Starling regarded the colon of carnivora chiefly as an excretory organ, since it played an important part in the elimination of calcium, magnesium, iron and phosphates, and he also mentioned that ulceration found in the large bowel following poisoning by mercury may be due to excretion of this drug by this route.

In his work on dogs, Draper<sup>153</sup> found that the right portion was relatively inactive as compared with the left portion in the excretion of various drugs and toxins. He noted that in poisoning by pilocarpine or diphtheria the mucosa of the proximal portion of the colon was bright scarlet, whereas that of the left portion remained normal. In 1929, Underhill, Peterman and Steel,<sup>154</sup> studying the fate of aluminum intravenously injected, found widespread elimination of the metal through the stomach and the small and large bowel. Borgen, Osterberg and Mann,<sup>155</sup> using dogs with colons isolated as previously described, except opening only at the cecal portion, studied the excretion of some of the heavy metals. They found that arsenic in the form of neoarsphenamine or meta-amino-para-oxyphenyl-arsenic acid, and mercury, mercurochrome and metaphen were excreted not at all or very little through

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151. Voit, Fritz: Beiträge zur Frage der Secretion und Resorption im Dünndarm, Ztschr. f. Biol. **29**:325, 1892.

152. Peola, Flora: Sulla funzione emuntoria dell' intestino crasso, Gazz. d. osp. **46**:1181, 1925.

153. Draper, J. W.: Studies in Intestinal Obstruction, with a Report of Feeding Heterologous Jejunal and Ileac Cells to a Human Being, J. A. M. A. **63**:1079 (Sept. 26) 1914.

154. Underhill, F. P.; Peterman, F. I., and Steel, S. L.: Studies in the Metabolism of Aluminum: IV. The Fate of Intravenously Injected Aluminum, Am. J. Physiol. **90**:52 (Sept.) 1929.

155. Borgen, J. A.; Osterberg, A. E., and Mann, F. C.: Absorption and Excretion of Arsenic, Bismuth and Mercury: Experimental Work on the Colon, Am. J. Physiol. **89**:640 (Aug.) 1929.



the colon. Bismuth, they noted, whether given by mouth or intramuscularly, was eliminated through the large intestine. Peola commented on the serious inflammation of the intestinal mucosa and especially of the colon in uremia, and stated that toxic materials are probably eliminated by this route. He quoted a number of observers whose experiments show that under pathologic conditions, such as that in which the kidneys are impaired, urica, salts and medicinal substances may pass through the intestines. Renon and Ricket<sup>156</sup> found that sugar could be eliminated in the intestine in diabetes, so much so as to cause diarrhea at times. No doubt this may account for some of the attacks of diarrhea experienced by diabetic patients. Peola, in acute experiments, using isolated loops of colon, injected methylene blue (methylthionine chloride, U. S. P.) intravenously and found it to be excreted partly by the kidney and partly through the colon. After ligating segments of both small and large bowel in the cat, Taylor and Fine<sup>157</sup> found only a small amount of calcium was excreted through either of these portions of the bowel, most of it coming through the kidneys.

*Ileocecocol Valve.*—A study of the physiology of the colon would not be complete without mention of the ileocecal valve or sphincter, and some of its functions. A comprehensive review of the literature will not be attempted, but merely a record of outstanding factors influencing or influenced by the large intestine. The importance of this sphincter is evidenced from the fact that certain observers have stated its proper function is just as essential to intestinal absorption as in the pylorus, and the former makes possible absorption of 95 per cent of the food before the cecum is reached. Alvarez quoted Rutherford and others as having observed in patients with cecal fistulas swaying movements associated with the to-and-fro contractions of the terminal portion of the ileum. About 4 cc. of semifluid feces came out of this sphincter in a jet every few moments; the lumen was enlarged and the circular fibers were relaxed. Viault and Jolyet<sup>158</sup> regard this act of the passage of excreta from the small into the large intestine as "internal defecation." Normally, this sphincter varied in tautness from the condition observed by Rutherford in which even a no. 12 French catheter could not be passed, to that observed by Short, in which he could easily insert his finger during relaxation. Macewen<sup>159</sup> was the first observer to be impressed with the sudden increase in activity of this sphincter after

156. Renon and Ricket, quoted by Peola: *Gazz. d. osp.* **46**:1181, 1925.

157. Taylor, N. B., and Fine, A.: *Excretion of Calcium Through the Intestine*, *Am. J. Physiol.* **93**:544 (June) 1930.

158. Viault and Jolyet, quoted by Luciani: *Human Physiology*, London, The Macmillan Company, 1913, vol. 2, p. 364.

159. Macewen, William: *The Function of the Caecum and Appendix*, *Lancet* **2**:995 (Oct. 8) 1904.

the taking of food, which Cannon<sup>13</sup> has shown initiates movements in the cecum and ascending colon. Hertz and Newton also saw that filling of the proximal portion of the large intestine generally took place passively and quite slowly, and in this manner, at times, considerable pressure was exerted when the chyme was forced through the sphincter. Berlatzky<sup>160</sup> and Hertz<sup>44</sup> noted great increase in the rate of passage of contents of the ileum into the colon with the taking of food.

*Ileocecal Sphincter.*—Alvarez observed that the function of this structure is to prevent the reflux of foul bacteria-laden contents of the colon, when absorption is slight, into the ileum where absorption is good, and to prevent too rapid passage of feces through the last segment of the small bowel. In event of the latter, no doubt diarrhea would often occur and symptoms of true auto-intoxication, whatever they may be, might be expected. As mentioned, the ileocecal sphincter is subject to reflexes such as the gastro-ileac or feeding reflex. Hinrichsen and Ivy<sup>161</sup> found that stimulation of the pyloric sphincter resulted in contraction of the ileocecal structure; likewise, distention of the stomach, duodenum, ileum or colon resulted in a similar action. In a large series of experiments they found that this sphincter may contract through either extrinsic or intrinsic mechanism. They found both motor and inhibitory fibers running to it from the vagus and motor fibers alone in the splanchnic system. Contraction of the sphincter resulted also from stimulation of both the hypogastric and pelvic nerves. They concluded that this is as true a sphincter as that of the pylorus, and that it stands in the same relation to the colon and small bowel as the pyloric sphincter does to the stomach and duodenum. The angle at which the ileocecal valve enters the colon has been the subject of much discussion because of the relationship it bears to intussusception. In cases in which there is disproportion in diameter of the two segments of bowel, along with excessive mobility, there is a tendency of the ileum to invaginate into the cecum.

This sphincter is no doubt of significance pathologically, both with reference to the digestive tract and the body in general. However, definite proof of a mechanism by which any influence of this nature takes place is lacking. Incompetence of the valve with regurgitation of the contents of the colon into the ileum has been blamed for many human ills, notably auto-intoxication, pernicious anemia, neurosis and epilepsy, yet, insufficiency of this sphincter seems to be present too often in normal individuals to lay the blame to such mechanism. Alvarez

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160. Berlatzky, quoted by Luciani: Human Physiology, New York, The Macmillan Company, 1913, vol. 2, p. 366.

161. Hinrichsen, J., and Ivy, A. C.: Studies on the Ileo-Cecal Sphincter of the Dog, Am. J. Physiol. 96:494 (Feb.) 1931.

stated that normally in about 60 per cent of the cases in which a barium enema is given some of it will run back into the ileum, and if the enema is big enough or the patient holds it long enough, it could always be made to flow back. This is certainly true of many of the laboratory animals, especially the dog. However, in the cat, this valve seems to be competent under considerable pressure, as Cannon,<sup>11</sup> Alvarez and others have noted. Weber<sup>162</sup> emphasizes the fact that distinction should be made between insufficiency and patency of the ileocecal valve. The former is found in practically all individuals when enough solution is introduced through the rectum, whereas patency usually occurs as a result of a pathologic condition, such as adhesions from chronic ulcerative colitis or chronic tuberculosis in that region. From a clinical standpoint, this distinction would seem of significance because it is almost invariably the rule that in cases of disease of the right third of the colon or of the terminal ileum, there is definite and sometimes severe secondary anemia. It would seem that there is more than a mere possibility that toxic substances could readily and constantly run back from the cecum, through the patent valve into the ileum, where absorption is notably facilitated. The sphincter seems to be a fairly efficient barrier to such regurgitation under normal conditions because great pressures are rarely present. However, a serious objection to this hypothesis lies in the fact that such anemia cannot be produced experimentally. In a series of dogs in which this valve was rendered incompetent by operative procedures, unusual variation in the hemoglobin and erythrocytes could not be detected in these animals during a period of fifteen months, in which estimations were made at least every ten days. It would seem that it is not possible to determine that insufficiency of this valve is of any etiologic significance in disease.

#### INNERVATION OF THE COLON: COLONIC SECRETION

Section of nerves to the colon seems to influence the character and amount of secretion as well as the movements of that organ. The nerve supply also is of importance in the evaluation of the experiments presented in this study.

The extrinsic nerves of the colon are derived in general from the two portions of the vegetative nervous system. Broadly speaking, the sympathetic nerves reach the wall of the bowel through the hypogastric and inferior mesenteric nerves, and the parasympathetic nerves enter by way of the pelvic nerve or *nervus erigentes*. The former in general are inhibitory to the muscular coats of the wall of the bowel and motor to the internal anal sphincter, whereas the pelvic nerve is motor to the colon and inhibitory to the sphincter of the anus. Most investi-

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162. Weber, H.: Personal communication to the authors.

gators are agreed that the vagus nerve takes little part in the innervation of the colon, yet there is some evidence, such as that by Boehm,<sup>163</sup> to suggest that in a few animals, the rabbit especially, the vagus does influence movements of the large intestine. The sympathetic innervation to the colon, according to Hovelacque,<sup>164</sup> is formed as follows: The superior mesenteric and semilunar ganglions surrounding the celiac axis supply the stomach, liver, spleen and small intestines and their blood vessels. Ganglions are also present adjacent to the renal arteries, the spermatic or ovarian vessels, which supply fibers proceeding along with vessels to the respective structures. The sympathetic nerves which pass to the colon have for their immediate origin the intercommunicating branches between the semilunar and celiac ganglions and the renal plexuses. The intermesenteric plexus descends in the median line and is joined on each side by the convergent branches from the first to the fourth lumbar ganglions, and these three roots form a more or less intricate plexus between the common iliac arteries called the presacral nerve (or plexus). In 20 per cent of cases the latter structure is a single nerve, and in 80 per cent it assumes a plexiform arrangement. At any rate, it descends into the pelvis and at the level of the first sacral vertebra divides into right and left hypogastric nerves, which join the corresponding ganglions where the cell stations of these fibers are situated. From there the postganglionic fibers of distribution pass to the pelvic viscera, lower part of the rectum and internal anal sphincter.

The inferior mesenteric nerves (sympathetic) supplying the greater part of the colon are formed as follows: Immediately below the level of the origin of the inferior mesenteric artery a large branch leaves the intermesenteric plexus of each side and passes inward on the aorta to reach the artery about 1.5 cm. from its origin. Finally, these two trunks unite and give rise to three or four large branches which course along the lateral borders of the vessels. They do not form a very close network around the vessel, nor are they closely attached to the vessel. From these nerves subsidiary trunks arise at the levels of the main divisions of the arteries and anastomose with one another in avascular parts of the mesosigmoid. From this network the final nerves of distribution are derived; their slender filaments cross juxtacolic vascular arcades and enter the wall of the bowel between the terminal branches of the vessels.

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163. Boehm, Gottfried: Ueber den Einfluss des Nervus vagus auf den Dickdarm, München. med. Wchnschr. **59**:1476 (July 2) 1912; Ueber den Einfluss des Nervus sympathicus und anderer autonomer Nerven auf die Bewegungen des Dickdarms, Arch. f. exper. Path. u. Pharmacol. **72**:1 (April 24) 1913.

164. Hovelacque, A.: Anatomie des nerfs craniens et rachidiens et du système grand sympathique chez l'homme, Paris, G. Doin & Cie, 1927.

Two or three large branches accompany the superior hemorrhoidal artery and invest the lateral and posterior walls in a plexiform manner. The distributions of the inferior mesenteric nerves correspond to those of the artery of the same name, and toward the end of the transverse colon where the left colic artery anastomoses with the middle colic branches of the inferior mesenteric plexus they communicate with filaments derived from the superior mesenteric plexus. The sympathetic innervation of the remainder of the colon is in dispute. Carlson<sup>165</sup> and also Cannon<sup>11</sup> are of the opinion that the transverse colon has no extrinsic nerves.

Whether the lumbar fibers which join the inferior mesenteric plexus to form the sacral nerve actually contribute functionally to the plexus is also disputed, and according to Learmonth and Braasch<sup>166</sup> is a question of great significance surgically in the treatment of Hirschsprung's disease. If they do not, as Delmas and Laux<sup>167</sup> hold, then lumbar ramisectomy and ganglionectomy, the operation favored by Hunter<sup>168</sup> and Royle<sup>169</sup> and by Judd and Adson,<sup>170</sup> would affect only that portion of the bowel innervated by the presacral nerve (lower part of the rectum and internal anal sphincter). But if they do contribute functionally, as Hovelacque contends, then the descending and sigmoid portions of the colon as well as the rectum and internal sphincter of the anus would be affected. Clinical experience favors the latter view.

In adult human beings there is no inferior mesenteric ganglion, although in the fetus and in the child it has occasionally been identified. When present, it is situated at the juncture of the two parts of the intermesenteric plexus after they have given off nerves to the colon. In the dog there is a definite inferior mesenteric ganglion and from this

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165. Carlson, A. J.: The Extrinsic Nervous Control of the Large Bowel, *J. A. M. A.* **94**:78 (Jan. 11) 1930.

166. Learmonth, J. R., and Braasch, W. F.: Resection of Presacral Nerve in the Treatment of Cord Bladder: Preliminary Report, *Surg., Gynec. & Obst.* **51**: 494 (Oct.) 1930.

167. Delmas, J., and Laux: Constitution, forme et rapports du nerf présacré, *Montpellier méd.* **49**:187 (May 1) 1927.

168. Hunter, J. I.: The Postural Influence of Sympathetic Innervation of Voluntary Muscle, *M. J. Australia* **1**:86 (Jan. 26) 1924; The Significance of the Double Innervation of Voluntary Muscle Illustrated by Reference to the Maintenance of the Posture of the Wing, *ibid.* **1**:581 (June 14) 1924; On the Choice of Procedure Adopted in the Operation of Ramisection for Spastic Paralysis, *ibid.* **1**:590 (June 14) 1924.

169. Royle, N. D.: The Operations of Sympathetic Ramisection, *M. J. Australia* **1**:587 (June 14) 1924.

170. Judd, E. S., and Adson, A. W.: Lumbar Sympathetic Ganglionectomy and Ramisectomy for Congenital Idiopathic Dilatation of the Colon, *Ann. Surg.* **88**:479 (Sept.) 1928.

ganglion pass the lumbar colonic nerves accompanying the inferior mesenteric artery and its branches.<sup>171</sup>

The internal anal sphincter in man is innervated by the thoracico-lumbar outflow in one or both of the following ways, according to Learmonth and Markowitz:<sup>171</sup> (1) by way of the inferior mesenteric nerves through the superior hemorrhoidal branches and branches from the hypogastric ganglions and (2) by way of the presacral nerve.

In dogs impulses pass from the inferior mesenteric ganglion through the lumbar colonic nerves or through the hypogastric nerves to this sphincter.

Bayliss and Starling<sup>7</sup> claim that the functional activity of the sympathetic nervous system to the distal part of the colon and rectum is unquestionably inhibitory. However, there is some doubt as to the nature of the impulses to the proximal part of the colon. Carlson stated that the hypogastric fibers to the ascending and transverse colon may be both inhibitory and motor in type, and the result of stimulation depends on the tonus or motor state of the bowel at the time of stimulation. That is, if the colon is atonic to begin with, stimulation will cause a powerful contraction, but if it is in a fair degree of tonus or rhythmic contraction, the tonus or mobility is decreased. This is true of dogs, but not necessarily so of man. Leman<sup>172</sup> agreed to this view, stating further that the depressor effect of these nerves occurs only in the presence of definite tonus of the musculature, and if such tonus is absent no demonstrable effect occurs from stimulation. The mechanism of this effect may possibly be a contraction of the vessels of the intestine. Ludlum and McDonald,<sup>173</sup> from studies on the movements of the colon by roentgenoscopy, and after atropinization, came to a similar conclusion, stating that the amplitude and postural tone of the large intestine are probably dependent on vagus sympathetic balance and may be altered by chemical substances such as atropine and physostigmine (eserine). Their studies, however, do not seem clearcut in that they do not take into account the range of normal movements of the colon. The sympathetic outflow to the internal anal sphincter is largely motor, according to Scott and Morton,<sup>174</sup> and stimulation of the right or left hypogastric nerves or the lumbar colonic nerve will cause con-

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171. Learmonth, J. R., and Markowitz, J.: Studies on the Function of the Lumbar Sympathetic Outflow: I. The Relation of the Lumbar Sympathetic Outflow to the Sphincter Ani Internus, *Am. J. Physiol.* **89**:686 (Aug.) 1929; Studies on the Innervation of the Large Bowel: II. The Influence of the Lumbar Colonic Nerves on the Distal Part of the Colon, *ibid.* **94**:501 (Sept.) 1930.

172. Leman, A. E.: Present Status of the Question of Peripheral Innervation of the Colonic Movements, *Kazan. med. zh.* **13**:171, 1930.

173. Ludlum, S. D., and McDonald, Ellice: The Large Intestine and Vagus Sympathetic Action by Atropin and Eserine, *M. J. & Rec.* **123**:228 (Feb. 17) 1926.

174. Scott, W. J. M., and Morton, J. J.: Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease, *J. Clin. Investigation* **9**:247 (Oct.) 1930.

tractions of that muscle. There are a few inhibitory fibers, as Learmonth and Markowitz<sup>171</sup> have shown, which has been demonstrated by the use of ergotoxin, a drug that paralyzes motor sympathetic fibers.

*Motor Nerves.*—The motor innervation of the colon is derived from the parasympathetic system through the pelvic nerves. The latter are formed by the union of the fibers of the anterior primary divisions of either the second, third or fourth sacral nerve which then divide into anterior and posterior branches, the posterior traversing, but not forming synapses in, the hypogastric ganglia, as do the hypogastric nerves. The posterior branch then reaches the surface of the large bowel in a plexiform manner, and this is similar to part of Auerbach's plexus of the small intestine. The latter, however, lies between the two layers of muscle. The anterior branch of the pelvic nerve reaches and innervates the bladder in an identical manner.<sup>172</sup>

Stimulation of the pelvic nerve results in contraction of both the circular and the longitudinal musculature; in the dog this makes the colon look like a cord. The nerve tires easily. Again, Carlson claims that these nerves supply only the distal segment and the cecum and ascending portions of the colon. He and Cannon<sup>12</sup> are inclined to believe that the transverse colon receives no extrinsic nerves. Leman, however, claimed from his studies that each muscle of the large intestine receives fibers from the sympathetic and from the parasympathetic system.

One would naturally expect the distal part of the colon to have a more potent motor innervation because of the physiology of that portion of the bowel and its better developed musculature, present for the purpose of strong contractions to evacuate the bowel. On the right side, or proximal part, of the colon where the contents are liquid and absorption is taking place, peristalsis and backward running waves of constriction are all the movements that ordinarily take place.

The internal anal sphincter relaxes on stimulation of the pelvic nerves according to Gaskell,<sup>175</sup> Bartle<sup>176</sup> and others, although the hypogastric nerves contain a few inhibition fibers, as Leman has stated. The depressor action of the sacral nerves is not limited to the sphincter but also extends to the adjacent portion of the rectum, and so the lower part of the rectum probably contains both types of fibers. Further stimulation of the peripheral segment of the divided sacral nerve leads to contraction of the lower segment of the rectum.

Clinically, the innervation of the colon is of importance in the treatment of Hirschsprung's disease and other types of idiopathic dilatations

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175. Gaskell, W. H.: *The Involuntary Nervous System*, London, Longmans, Green & Co., 1920.

176. Bartle, H. J.: Megacolon: A Résumé of the Literature and Report of a Case; Ramisection Proposed as a Form of Treatment, *Am. J. M. Sc.* **171**:67 (Jan.) 1926.

of the colon.<sup>177</sup> By interruption of the inhibitory impulses through cutting the presacral nerve, or by lumbar ramisectomy and ganglionectomy, the motor nerves are left in less disputed control, and at the same time the opposition to the expulsion of the contents of the bowel offered by the internal anal sphincter is removed.

That the nervous system does influence the secretion of mucus in situations other than in the colon is no doubt true. Barrington,<sup>178</sup> by stimulation of the hypogastric nerve of a cat, obtained increased secretion of mucus from Bartholin's glands. He considered the gland to be situated deeply enough so that it was not influenced by events taking place in nearby viscera. Moreover, as is true with the salivary gland, psychic influences are capable of inciting secretion of the gland. The large amounts of mucus present in mucous colitis may be due to the intervention of the nervous system analogous to that found in the salivary and Bartholin's glands, but this point is still in doubt. It is also stated that it is hardly relevant to argue from one case to another, owing to different anatomic relationships and histologic appearance of the mucus cells in the various situations.

In a careful study, Florey<sup>179</sup> found that stimulation of either the sympathetic or the parasympathetic nerves was without effect on the amount of mucus secreted by the colon. He used Thiry fistulas made in the central portion of the distal end of the large intestine, and by biopsy several months after the operation found that the mucosa was indistinguishable from the normal. He also used a patch of colon entirely separated from the mesentery, and this continued to secrete mucus as it would ordinarily. In another series of experiments he tried to demonstrate nerve fibers to the mucus-secreting cells by many different methods but was unable to do this, concluding that these cells had no nerve fibers coming to them because by the same methods he could see innervating fibers to other glandular tissues, such as the pancreas and salivary glands. Florey summarized the evidence against nervous control of the goblet cells as follows: (1) The secretion of mucus is normal after section of nerves to the colon; (2) the secretion of mucus from a Thiry fistula is small and at a constant rate; (3) tissue cultures from chicken intestine show goblet cells developing and producing mucus; (4) on histologic examination nerves are not demonstrated, as in the case of the salivary glands, and (5) colonic secretion

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177. Rankin, F. W., and Learmonth, J. R.: Section of Sympathetic Nerves of the Distal Part of the Colon and the Rectum in the Treatment of Hirschsprung's Disease and Certain Types of Constipation, *Ann. Surg.* **92**:710 (Oct.) 1930.

178. Barrington, F. J. F.: The Variations in the Mucin Content of the Bulbo-Urethral Glands, *Internat. Monatschr. f. Anat. u. Physiol.* **30**:1, 1914.

179. Florey, H.: The Secretion of Mucus by the Colon, *Brit. J. Exper. Path.* **11**:348 (Oct.) 1930.



is not obtained from stimulation of nerves. In this connection Florey commented that the increased amounts of mucus seen in mucous colitis do not seem to be due to nervous excitation. He is of the opinion that increased secretion of mucus is due to injury to cells resulting either from direct trauma to the goblet cells or from liberation of a chemical substance which stimulates the goblet cells. However, Wood,<sup>180</sup> by sectioning the vagi, obtained decreased amounts of secretion in both small and large intestines even after administration of purgatives, but Hay<sup>120</sup> stated that this could not be, as he claimed not to have obtained a change after section of nerves. Moreau divided the mesenteric sympathetic nerves and thought he obtained increased amounts of mucus from the bowel. Hay interpreted these observations as due to an inhibiting action of the sympathetic system on secretion and an excitatory action on absorption, the total quantity depending on a balance between the nerves. Any influence which may increase or lessen purgative action may do this by affecting the rate of secretion or absorption.

Heupke<sup>181</sup> summarized the present knowledge of the secretion and excretion of the colon. Using a Thiry-Vella type of fistula on a dog, he found inorganic components such as potassium, calcium, magnesium and phosphoric acid always present, and these made up about 25 per cent of the total weight of dried secretion; 75 per cent was made up of organic compounds, mainly mucus, but also small quantities of purine bases and occasionally amino-acids. Urea, creatinine, cholesterol, and indole, skatol and other products of putrefaction were not present. Fermentative action was so slight that for practical purposes it can be disregarded. Of eleven coal tar dyes, given by subcutaneous or intravenous routes, none was excreted by the colon, and by the use of medicaments in a similar manner, it was found that iodine, bromine and potassium thiocyanate were recovered in small amounts in the isolated colon. Potassium ferrocyanide, quinine and gallic acid were not recovered from the secretion of the colon.

Some work which we have done on the secretory activity of the colon of the dog, isolated within the abdominal cavity, will be reported in a subsequent paper. Therein reference will be made to work of Drury, Florey and Florey, Hertz, Cook and Schlesinger,<sup>182</sup> Florey, and Harvey.<sup>183</sup>

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# TREATMENT OF SECONDARY ANEMIA IN GYNECOLOGIC PATIENTS

HOUSTON S. EVERETT, M.D.

BALTIMORE

Secondary anemia following excessive uterine hemorrhage constitutes a frequent and important complication of gynecologic disorders. When the bleeding is the result of such gross lesions as uterine fibroids, a severe degree of anemia may present a situation requiring considerable delicacy of judgment in its handling. A major surgical procedure is usually necessary to stop the excessive flow effectively and permanently, and before the surgeon is justified in operating the anemia must be effectively treated to an extent sufficient to render the procedure a safe risk; this must usually be accomplished in the all too brief interval between two prolonged and profuse menstrual periods. It is therefore essential that one have at one's disposal efficient and speedy methods of effecting such an improvement.

For many years iron in one form or another has been the standard drug used in the treatment of such conditions, and more recently transfusion has proved to be of tremendous help. The past six years, however, have constituted a period of flux in the treatment of secondary anemia, stimulated largely by the epoch-making work of Minot and Murphy in the treatment of pernicious anemia with liver and liver extracts. So enthusiastic has been the acceptance of liver as a panacea, and so widespread its adoption in the treatment of various types of anemias, that it has quickly risen from a lowly position as one of the butcher's cheaper wares to that of an expensive drug, thus economically handicapping the victims of primary anemia to whom its use is essential.

Is this indiscriminate use of liver essential? It seems time to pause and compare carefully the results of liver therapy with those obtained by other methods, and at the same time, if possible, determine the speediest and most efficient method at one's disposal. In an attempt to do this I have reviewed and analyzed the records of all patients admitted to the gynecologic service of the Johns Hopkins Hospital from Jan. 1, 1926, to May 1, 1931, in whom the hemoglobin on admission was 50 per cent or below. There were 305 such patients, constituting 4.6 per cent of the 6,570 total admissions to the service during the same period. Of these, 233 were colored and 72 were white in a service that admits about equal numbers of the two races.

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Read before the Baltimore City Medical Society, Feb. 19, 1932.

From the Department of Gynecology of the Johns Hopkins Hospital and University.

The degree of anemia in these 305 patients is indicated in table 1.

The lowest amount of hemoglobin in the series was 10 per cent. This patient was suffering from an advanced inoperable carcinoma of the cervix; she was given a blood transfusion and was discharged with a hemoglobin of 35 per cent after seventeen days on a liver diet and pills of ferrous carbonate, U. S. P. The cervix was cauterized to control the bleeding, but the patient was considered by both surgeons and radiologists to be beyond the stage of possible real benefit either from surgery or irradiation.

#### ETIOLOGY OF ANEMIA

Table 2 shows the relative frequency of the various gynecologic disorders which had preceded the anemia. This table requires only

TABLE 1.—*Distribution of Patients According to Degree of Anemia*

Hemoglobin, per Cent (Sahli)	Number of Patients
10-20.....	16
21-30.....	44
31-40.....	81
41-50.....	164

TABLE 2.—*Frequency of Various Gynecologic Conditions Which Acted as Contributing Causes of Anemia*

Diagnosis	Number of Cases
Myomata uteri.....	138
Endometrial hyperplasia and bleeding without determined anatomic lesion....	57
Carcinoma of the cervix.....	27
.....nditions.....	19
.....disease.....	24
Tubal pregnancy.....	11
Incomplete abortion.....	9
Tuberculosis of pelvic.....	4
Tuberculosis of the kidney.....	1
Miscellaneous diagnoses.....	15

brief comment. As would be expected, uterine myomas with associated bleeding due to submucous nodules constitute by far the largest group. Endometrial hyperplasia and similar conditions, because of the absence of any gross pathologic lesion, are not as a rule considered serious, but it is seen here that they are probably the etiologic factors in the second largest group of anemias. The 19 patients with malignant conditions other than carcinoma of the cervix include 2 with adenocarcinoma of the body of the uterus, 3 with sarcomatous degeneration of myomas, 4 with hypernephroma and 3 with carcinoma of the bladder. All these showed external loss of blood, either through excessive uterine bleeding or hematuria, in addition to general debility from the disease. In the other patients, 5 with carcinoma of the ovary, 1 with pseudomyxoma peritonei and 1 with carcinoma of the tube, the anemia was merely one of the many manifestations of the ravages of the disease.

The 24 patients listed as suffering from pelvic inflammatory disease all afforded examples of the severer forms of this condition such as pelvic abscess, tubo-ovarian abscess and pelvic peritonitis. In some of these bleeding was a factor, but in the majority the anemia was largely a part of the general debility associated with a severe inflammation. The same was true of the tuberculous patients. Pelvic inflammatory disease in the chronic form was also associated with many of the

TABLE 3.—*Diagnosis, Per Cent of Hemoglobin and Operation in Fatal Cases*

Diagnosis	Hemoglobin, per Cent	Operation	Cause of Death
1. Recurrent carcinoma of cervix; ureteral obstruction	30	None	Uremia
2. Pseudomyxoma peritonei . . . . .	50	Exploratory laparotomy	Shock
3. Sloughing submucous myoma; bilateral femoral thrombophlebitis	33-16	Vaginal myomectomy	Phlebitis
4. Adenocarcinoma of corpus uteri . . . . .	50	Panhysterectomy	Shock
5. Myomata uteri; intracranial hemorrhage	25	None	Intracranial hemorrhage
6. Infected myoma; pulmonary emboli; lung abscess	30	None	Transfusion reaction
7. Sarcoma of ovary . . . . .	50	Exploratory laparotomy	Shock
8. Myoma; sarcomatous degeneration with metastases	40	None	
9. Carcinomatosis; adenocarcinoma of ovary	53-57	Exploratory laparotomy	Shock
10. Tuberculous salpingitis and peritonitis; pulmonary tuberculosis	50	Exploratory laparotomy	
11. Myomata uteri; bilateral tubo-ovarian abscess	50-53	Hysterectomy; bilateral salpingo-oophorectomy	Pneumonia; peritonitis
12. Recurrent carcinoma of ovary; carcinomatosis	50	None	
13. Pelvic abscess communicating with sigmoid; generalized peritonitis	50	Posterior colpotomy	Infection; inanition
14. Nephrolithiasis; pyonephrosis . . . . .	35	Nephrectomy	Collapse
15. Tuberculous salpingitis and peritonitis..	39-28	Posterior colpotomy	Pneumonia
16. Myomata uteri; peculiar infection of uterus and pancreas	25	None	Intracranial hemorrhage

myomas but was not usually considered an important factor in the production of the anemia, for this was directly attributable in most cases to bleeding from a submucous myomatous nodule.

#### SURGICAL TREATMENT AND RESULTS

Dr. Thomas S. Cullen, in 1913, reported the cases of 170 patients with a hemoglobin of 40 per cent or below treated in the gynecologic service up to that time. Among these 170 patients there were 20 deaths, but in 7 of these cases no operation was performed, the condition being considered hopeless, and in 9 others the operation was for an advanced

malignant condition, so that the mortality was for the most part among absolutely hopeless cases. In the present series of 305 patients all but 33 underwent some form of operation. There were 147 laparotomies, usually for hysterectomy, 119 minor procedures, among which are included vaginal removal of submucous myomas, and 6 operations on the kidney. On discharge, 146 patients were well, 126 improved and 17 unimproved, and there were 16 deaths. Many of the patients classified as improved might have been considered well except for the fact that it is a conservative rule of the service to classify as improved patients suffering from such conditions as endometrial hyperplasia in which the symptoms are apt to recur.

The 16 deaths give a mortality for the series of 5.25 per cent as compared with a total mortality in the service during the same period of 1.83 per cent. The majority of the deaths, however, were in patients in an absolutely hopeless condition on entering the hospital, 5 of whom

TABLE 4.—*Postoperative Complications*

Complication	No. of Cases	Complication	No. of Cases
Hyperpyrexia.....	11	Secondary hemorrhage.....	2
Bronchopneumonia.....	8	Fecal fistula.....	1
Thrombophlebitis.....	7	Hemiplegia.....	1
Pyelitis.....	6	Intestinal obstruction.....	1
Shock.....	4	Peritonitis.....	1
Infected incision.....	3	Cystitis.....	1
Pelvic abscess.....	2		

could not be operated on, as will be seen by reference to table 3. There were 2 patients, numbers 3 and 14 in the table, in whom perhaps transfusion might have been of life-saving benefit, but in each of these instances every possible effort was made to obtain suitable donors without success.

#### POSTOPERATIVE COMPLICATIONS

Postoperative complications, particularly thrombophlebitis, occurred less frequently in this series than I had anticipated. In gynecologic operations at this hospital we are constantly on the lookout for this complication, and particularly so among the anemic patients, and I was rather surprised to find that it occurred only 7 times in the 305 cases. Table 4 shows the relative frequency of various postoperative complications in the series.

#### TREATMENT OF ANEMIA

The use of liver for secondary anemia was begun in the service in the fall of 1926 by Dr. R. Glen Craig, the resident at that time. Prior to this the treatment had been the administration of a nourishing, high caloric diet, with elixir of iron, quinine and strychnine to stimulate the

appetite, and pills of ferrous carbonate from 10 to 15 grains (0.65 to 0.972 Gm.) three times a day. Transfusions were also frequently employed. Liver then came into vogue and was used in quantities of 200 Gm. a day added to a diet similar to that previously used. In a small series of cases no iron was used in order to determine accurately, if possible, the beneficial effect of liver per se, but in the majority of the cases in my series iron, quinine and strychnine and pills of ferrous carbonate have also been given. For the first few months after the introduction of liver, transfusions were used less frequently, but because of their unquestioned effectiveness, and particularly because of their

TABLE 5.—*Changes in the Percentage of Hemoglobin Following the Several Types of Treatment*

Treatment	Number of Cases	Average Rise in Hemoglobin, per Cent	Average Number of Days
None .....	21	2	22
Amplified diet; iron, quinine and strychnine; pills of ferrous carbonate .....	8	25	25
Liver diet; iron, quinine and strychnine; pills of ferrous carbonate .....	22	20	24
Liver diet without iron.....	12	10	25
Transfusion alone .....	6	14	8
Two transfusions .....	12	37	13
Transfusion; amplified diet; iron, quinine and strychnine; pills of ferrous carbonate.....	15	22	19
Transfusion; liver diet; iron, quinine and strychnine; pills of ferrous carbonate.....	27	24	21
Liver extract; iron, quinine and strychnine; pills of ferrous carbonate .....	13	13	19
Transfusion; liver extract; iron, quinine and strychnine; pills of ferrous carbonate.....	10	25	20
Iron ammonium citrate.....	6	15	16
Transfusion; iron ammonium citrate.....	4	24	19
Severe infection or advanced malignant condition treated without transfusion .....	29	2	23
Severe infection or advanced malignant condition treated with transfusion .....	12	13	23

importance as a time-saving factor, their use, wherever possible, was quickly resumed. Within the last two years liver has been replaced to some extent by liver extract given in quantities of 30 cc. three times a day.

Beginning about Oct. 1, 1930, Dr. Beebe and Dr. Wintrobe of the medical service, who were studying secondary anemias in general, treated a small series of gynecologic patients with iron ammonium citrate, 2 cc. of the crystals dissolved in a glass of milk three times a day.

Table 5 shows in composite form the results obtained with these various forms of treatment. Of the 305 cases, 197 were used in compiling this table. In the other cases the period of observation was too brief or the number of hemoglobin determinations too few to admit of accurate conclusions. I must emphasize the fact that the figures are all averages and should not be taken too literally, but with this reser-

vation in mind the following conclusions may be drawn: Some form of special treatment seems to be necessary to obtain a rise in hemoglobin. In the 21 patients not treated for anemia, that is, who were put on ordinary ward diet without administration of iron, there was practically no average rise in hemoglobin over an average period of twenty-two days. The older treatment with a nourishing high caloric diet in combination with iron, quinine and strychnine and pills of ferrous carbonate apparently gave as good results as were later obtained with the addition of liver or liver extract. Liver without iron was less than half as efficient as all forms of diet with iron. All forms of diet with iron succeeded in raising the average of the hemoglobin slightly less than 1 per cent a day, while the same types of treatment with transfusion raised the hemoglobin in each case a little more than 1 per cent a day. A single transfusion in 6 cases is seen to have produced a rise of almost 2 per cent a day, while with two transfusions there was a rise of more than 2 per cent a day. The chief asset of transfusion in the cases of simple bleeding, therefore, seems to be a time-saving element. In fact, if the 14 per cent average rise in hemoglobin following transfusion alone had been based on determinations made the day before and the day after transfusion, the whole rise would probably have been found to occur during this period, but the average of eight days represents the time consumed after admission before a suitably matched donor with a negative Wassermann reaction could be obtained. This difficulty in securing donors is frequently encountered for colored patients. Similarly, those patients who had two transfusions were admitted with profound anemia, and on an average eighteen days were consumed in preparing for and giving two transfusions and other stimulative measures before any operative procedure was considered to be advisable.

The last two items of table 5 show strikingly the value of transfusion in combating the anemia resulting from wasting debilitating diseases. Here it was found to be the only method that was effective to any appreciable degree.

The accompanying charts represent graphically the results in specific cases of several of the foregoing methods of treatment. The charts are for the most part self-explanatory, but it may be stated that in the patient represented in chart 8 the secondary hemorrhage followed removal of the skin sutures on the eighth day following operation. This is an example of the fact frequently observed that healing proceeds more slowly in anemic patients, and serves to emphasize the fact that greater care and delay should be exercised in removal of the sutures in this type of case.

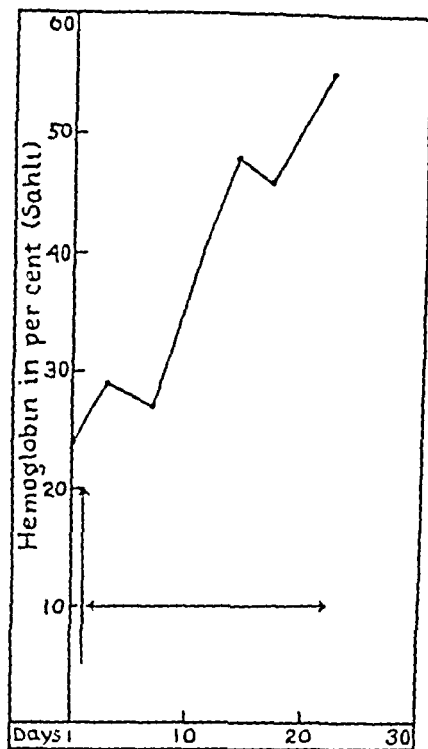


Chart 1 (unit no. 1824).—Rise in hemoglobin produced by a high caloric diet and iron. The patient was admitted on Jan. 4, and discharged on Jan. 27, 1927. The diagnosis was metrorrhagia and cervical polyp. Dilatation and curettage were performed. The vertical arrow indicates the date of operation; the horizontal arrow, the period over which the patient received a 4,000 calory diet, elixir of iron, quinine and strychnine, 8 cc. three times a day, and pills of ferrous carbonate, 0.3 Gm. three times a day.

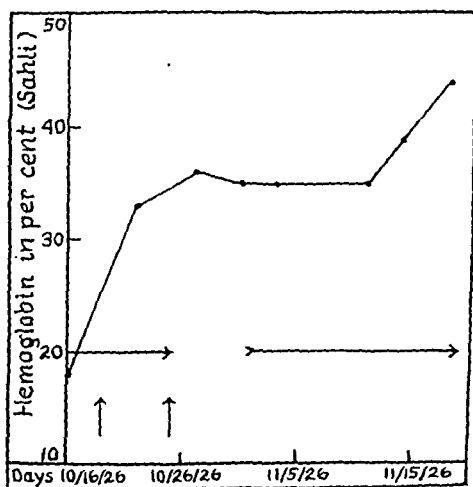


Chart 2 (unit no. 8328).—Effect on hemoglobin of transfusion and of a liver diet without iron. The patient was admitted on Oct. 16, and discharged on Nov. 19, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy was performed. The two horizontal arrows indicate the periods over which the patient received a Murphy-Minot diet; the first vertical arrow, the date of transfusion of 550 cc. of citrated blood, and the second vertical arrow, the date of operation.



Hemoglobin in per cent (Sahl.)

Days 1 10 20 30

Chart 3 (unit no. 23985).—Effect on hemoglobin of a liver diet and iron. The patient was admitted on April 2, and discharged on May 20, 1929. The diagnosis was myomas of the uterus with submucous nodule. Panhysteromyomectomy and bilateral salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with 150 Gm. of liver daily, elixir of iron, quinine and strychnine, 5 cc. three times a day, and pills of ferrous carbonate, 1 Gm. three times a day; the block in the lower left corner, a daily hypodermic injection of 1 cc. of sodium cacodylate, and the vertical arrow, the date of operation.

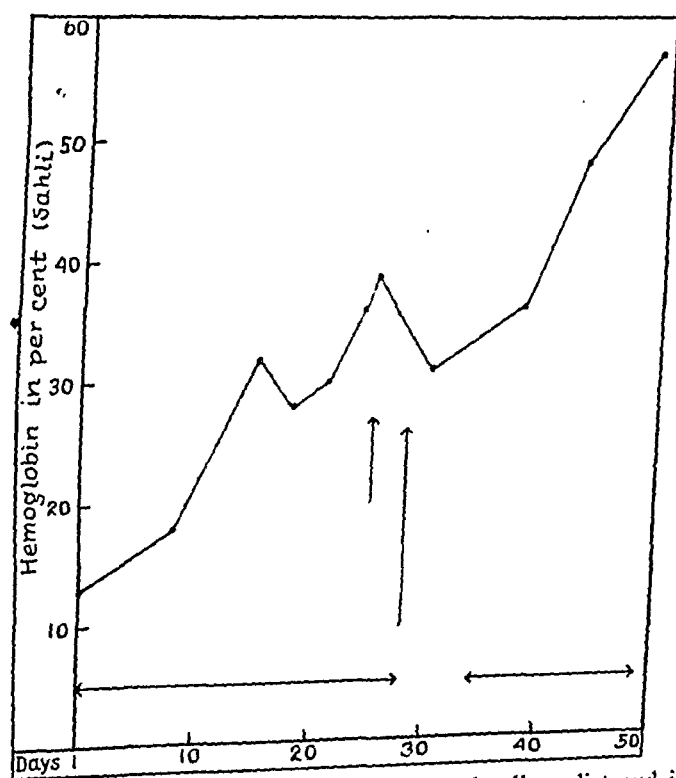


Chart 4 (unit no. 8220).—Effect on hemoglobin of a liver diet and iron. The patient was admitted on Oct. 11, and discharged on Dec. 1, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy, right salpingo-oophorectomy and appendectomy were performed. The horizontal arrows indicate the periods over which the patient received Murphy-Minot diet and pills of ferrous carbonate, 0.3 Gm. three times a day; the first vertical arrow, the onset of profuse menstruation, and the second vertical arrow, the date of operation.

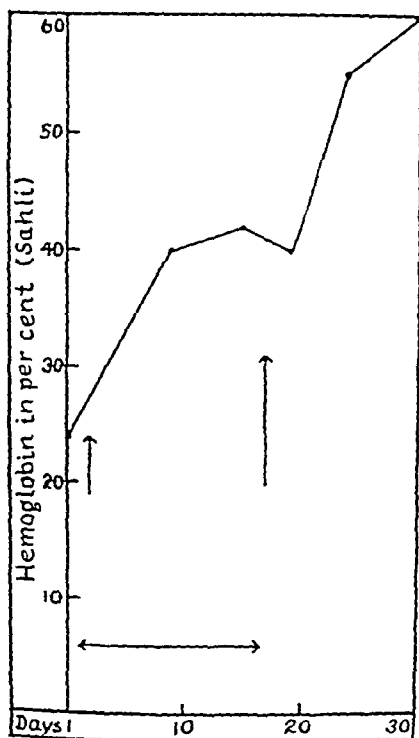


Chart 5

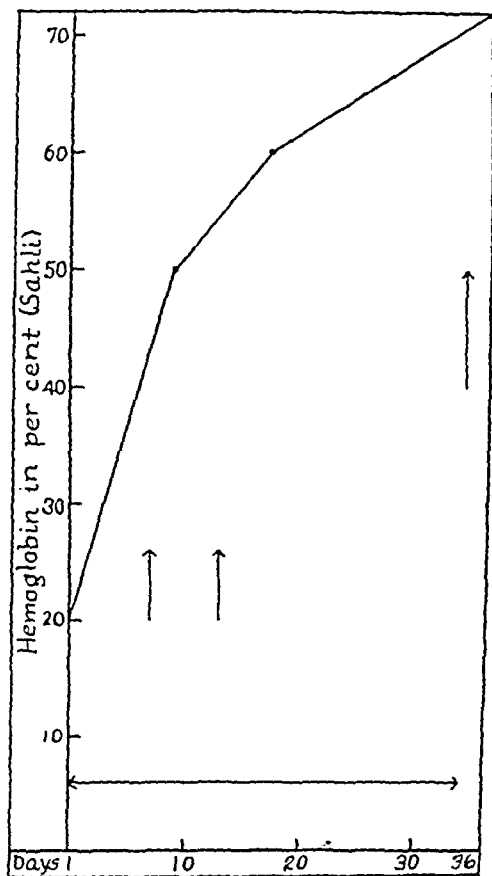


Chart 6

Chart 5 (unit no. 4787).—Effect on hemoglobin of transfusion, amplified diet and iron. The patient was admitted on May 12, and discharged on June 17, 1926. The diagnosis was myomas of the uterus. Hysteromyomectomy and left salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with elixir of iron, quinine and strychnine, 4 cc. three times a day, and pills of ferrous carbonate, 0.3 Gm. three times a day; the first vertical arrow, transfusion of 400 cc. of citrated blood, and the second, the date of operation.

Chart 6 (unit no. 34377).—Effect on hemoglobin of two transfusions, liver extract and iron. The patient was admitted on Dec. 2, 1930, and discharged on Jan. 24, 1931. The diagnosis was myomas of the uterus, chronic salpingitis and cardiac hypertrophy. Hysteromyomectomy, left salpingo-oophorectomy and appendectomy were performed. The first two vertical arrows indicate transfusions of citrated blood, 650 cc. each; the horizontal arrow, the period over which the patient received liver extract, 30 cc. twice daily, elixir of iron, quinine and strychnine, 5 cc. three times a day before meals, and pills of ferrous carbonate, 0.6 Gm. three times a day after meals, and the third vertical arrow, the date of operation.

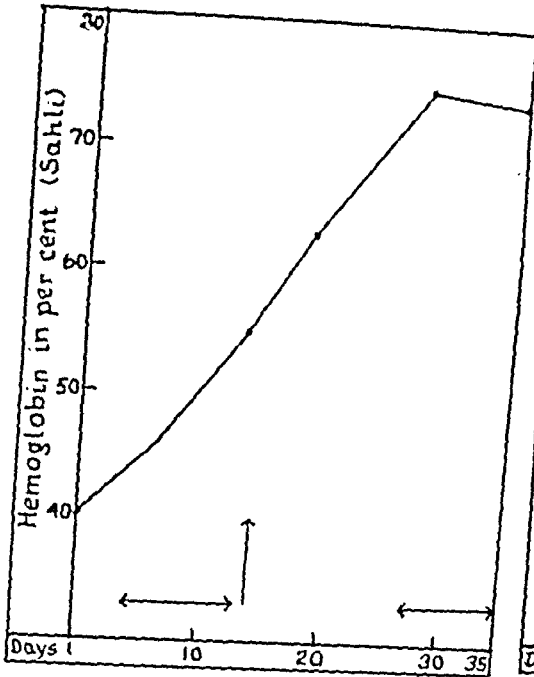


Chart 7

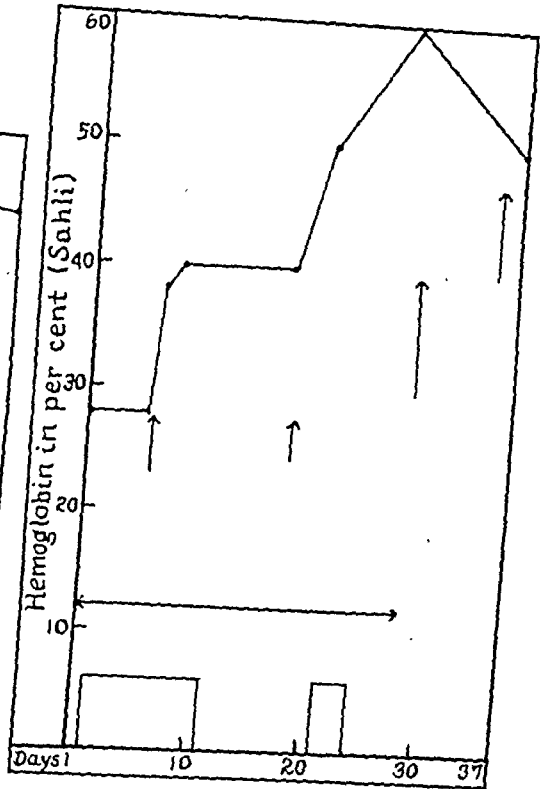


Chart 8

Chart 7 (unit no. 12587).—Effect on hemoglobin of iron ammonium citrate. The patient was admitted on Dec. 2, 1930, and discharged on Jan. 7, 1931. The diagnosis was myomas of the uterus. Hysteromyomectomy and appendectomy were performed. The patient received 2 cc. of crystals of iron ammonium citrate dissolved in a glass of milk three times a day over the periods indicated by the horizontal arrows. The date of operation is indicated by the vertical arrow.

Chart 8 (unit no. 26672).—This chart illustrates in a striking manner the inefficiency of dietary and medicinal treatment as compared with transfusion in cases complicated by infection. The patient was admitted on Sept. 3, and discharged on Oct. 27, 1929. The diagnosis was myomas of the uterus and tubo-ovarian abscess (right). Hysteromyomectomy and bilateral salpingo-oophorectomy were performed. The horizontal arrow indicates the period over which the patient received an amplified diet with 150 Gm. of liver daily and pills of ferrous carbonate, 1 Gm., three times a day; the two blocks at the bottom of the chart, the daily hypodermic administration of 1 cc. of sodium cacodylate; the first two vertical arrows, transfusions of 650 and 800 cc. of citrated blood. Note the sharp rise following each of these with the practically flat curve between the two. The third vertical arrow indicates the date of operation, and the fourth, a secondary hemorrhage necessitating a secondary closure of the abdominal incision and accounting for the fall in hemoglobin at the end of the chart.

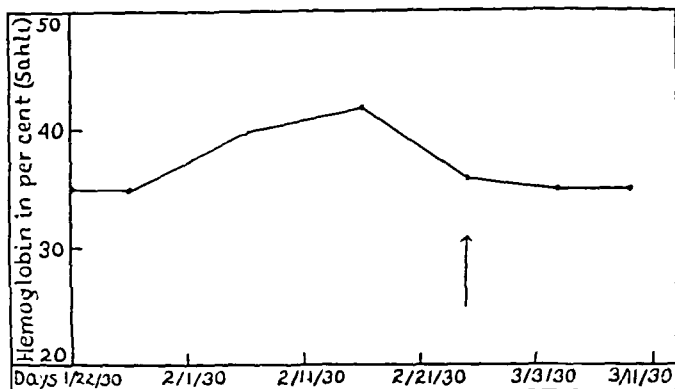


Chart 9 (unit no. 27363).—The inadequacy of dietary and medicinal treatment in a patient in whom the anemia was due to infection rather than hemorrhage. The patient was admitted on Jan. 22, and died on March 11, 1930. The diagnosis was left nephrolithiasis and pyonephrosis. Left nephrectomy was performed. The patient died of shock on the day of operation. The patient received an amplified diet with 200 Gm. of liver daily with elixir of iron, quinine and strychnine, 5 cc. three times a day before meals, and pills of ferrous carbonate, from 0.6 to 1 Gm. three times a day throughout her course in the hospital. The arrow indicates the time when the dosage of ferrous carbonate was increased to 1 Gm.

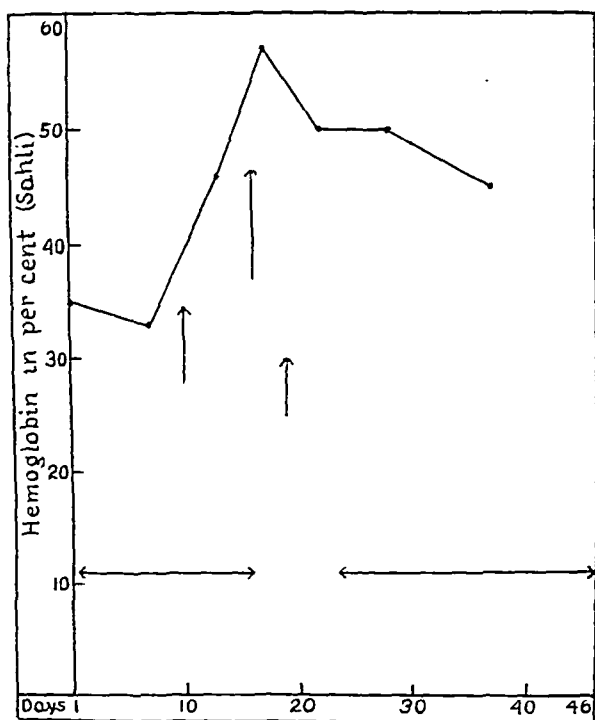


Chart 10 (unit no. 20713).—Detrimental effect on rise in hemoglobin produced by thrombophlebitis. The patient was admitted on Sept. 17, and discharged on Nov. 2, 1928. The diagnosis was myomas of the uterus and chronic salpingitis. Hysteromyomectomy, bilateral salpingo-oophorectomy and appendectomy were performed. The two horizontal arrows indicate periods over which the patient received an amplified diet with 200 Gm. of liver daily, elixir of iron, quinine and strychnine, 5 cc. three times a day, and pills of ferrous carbonate, 0.3 to 1 Gm. three times a day. The first vertical arrow indicates transfusion of 500 cc. of citrated blood; the second vertical arrow, operation and simultaneous transfusion of 460 cc. of citrated blood, and the third vertical arrow, the onset of the thrombophlebitis.

## CONCLUSIONS

From the study of the foregoing figures, I believe that the following conclusions are justified:

1. Secondary anemia, though a frequent and often annoying complication in gynecologic surgery, by careful preoperative and post-operative treatment may be rendered relatively innocuous so far as any perceptible increase in hazard to the patient is concerned.

2. Transfusion is the treatment par excellence in such cases, and in patients suffering from a wasting, debilitating type of disease it would seem to be the only type of treatment that produces any appreciable benefit, and even this procedure is not advisable in cases of inoperable malignant conditions in which radium offers no hope.

3. If sufficient time is available, very good results may be obtained in the simple anemias resulting from bleeding by the use of a nourishing amplified diet together with iron, either pills of ferrous carbonate or iron ammonium citrate.

4. The addition of liver to the diet probably has a slightly beneficial effect, but this is not sufficient to render its use essential, and it would probably be better to reserve the supply for the economic benefit of sufferers from pernicious anemia.

101 West Read Street.

# EPIDERMOID CYSTS OF THE SPLEEN

HAROLD K. SHAWAN, M.D.

DETROIT

Epidermoid cysts of the spleen have rarely been reported. A patient whom I have followed up for ten years after splenectomy had a megalo-splenic cyst lined in part by a stratified epidermoid structure. This case will be discussed before a review of the cases so far described in the literature is presented.

## REPORT OF A CASE

*History.*—V. N., a white girl, aged 16, entered the Detroit Receiving Hospital on June 20, 1922, with the complaint of a gradual enlargement of the upper left part of the abdomen during the preceding two and one-half years. There had been an occasional slight local pain which was referred to the left shoulder. Once, about four months before, there was a sudden, sharp, severe pain in the region of the enlargement, accompanied by a marked degree of dyspnea. This was followed by a chill and a temperature of 104 F. The fever gradually subsided, and in a week the temperature was normal. There were no other acute symptoms. Shortness of breath on exertion had increased moderately. There had been no nausea or vomiting, no feeling of fullness after meals and no loss of appetite. There were no intestinal or urinary complaints. A loss of 7 pounds (3.2 Kg.) during the two months preceding admission to the hospital was attributed to a continuous round of good times.

The patient had had the usual children's diseases, with diphtheria, tonsillitis and smallpox. She had had an appendectomy and drainage of an appendiceal abscess five years before. Her menses began at the age of 11 and were never very regular. The last period was nearly two months before admission to the hospital. However, there had been no radical change in this function since the onset of the present complaint. A severe injury to her left side during childhood was not recalled until some days after splenectomy.

*Physical Examination.*—The general physical report, being irrelevant, will be omitted. The left costal margin flared markedly. In the upper left quadrant of the abdomen there was a mass which moved with respiration. It was smooth, soft and fluctuant, and was not tender to palpation. The rounded lower border curved from the tip of the left eleventh rib across the abdomen, just above the umbilicus, and disappeared behind the eighth left costal cartilage. No notch was felt.

*Laboratory Tests.*—Analysis of the blood showed: hemoglobin, 75 per cent; red cells, 4,010,000; white cells, 5,800. The differential white count showed: 67 per cent polymorphonuclears, 3 per cent large mononuclears, 26 per cent small mononuclears and 4 per cent eosinophil cells. The nonprotein nitrogen was 35 mg. per hundred cubic centimeters of blood. The blood sugar was 0.235 per cent. The Wassermann reaction of the blood was negative. The urine was normal.

*Roentgen Examination.*—The findings in the chest and the gastro-intestinal tract were reported by Dr. H. B. Doub as follows: The stomach and the lower portion of the esophagus are crowded over toward the right side beyond the midline.

The palpable mass in the left side of the abdomen causes a rounded incurving on the greater curvature of the stomach, but there is no involvement of the stomach. Most of the small bowel in the upper part of the abdomen seems to be present in the right side, but no organic pathologic condition is seen. The splenic flexure and transverse colon are displaced downward by the mass on the left side. No evidence of any involvement of the colon is seen. No pathology is seen in the chest with the exception of a slight elevation of the left diaphragm. The deformity seen seems to be due to pressure by the mass in the left upper quadrant of the abdomen, which appears to be the spleen.

*Operation and Course.*—On June 27, a vertical, upper, left, rectus, abdominal incision was made, and the mass described was found to be a splenic cyst. A trocar was inserted into this cyst, and 1,500 cc. of fluid was drained off. After freeing a few adhesions to the diaphragm and the abdominal wall about the costal margin and after multiple ligations of the pedicle, the spleen, together with the collapsed walls of the cyst, was removed. A small tip of the tail of the pancreas



Fig. 1.—A photograph of the exterior of the cyst. Note (A) splenic pedicle, (B) splenic border and (C) membranous wall of the cyst.

was accidentally included in the pedicle ligatures. There was practically no bleeding, and after removal of the spleen no point of oozing was found. The liver, ovaries and other intra-abdominal organs appeared to be normal. The incision was closed in layers without drainage.

Convalescence was uneventful. Routine laboratory reports were all within range of normal, except that for several days there was a small amount of sugar in the urine. The blood sugar dropped from 0.235 to 0.153 per cent, but three days later had returned to normal. The patient was discharged from the hospital seventeen days after operation.

*Follow-Up Report.*—Thenceforth the patient was seen from time to time and had no important complaints or findings. In September, 1931, nine years after operation, she was more completely studied. Her healthy-appearing baby, normally born, after an uncomplicated pregnancy, was 25 months old at the time. The patient had had some vague upper abdominal pains. Physical examination showed a well healed left rectus incision, some tenderness over the gallbladder, barely

palpable inguinal glands and a slight enlargement of the thyroid. Examination of the blood showed no important changes from the findings before operation. The blood calcium was 12 mg. and the blood cholesterol 160 mg. per hundred cubic centimeters of blood. Roentgenograms of the gastro-intestinal tract revealed no pathologic changes; the gallbladder was visualized, and it emptied within normal limits.

*Pathologic Report.*—The specimen, in the preserved state, was ovoid and measured 22 by 17 by 12 cm. (fig. 1). The color was grayish blue. The blood vessels showed no gross changes. Most of the splenic tissue was flattened at the



Fig. 2.—Drawing of the interior of the cyst, showing trabeculae and recesses beneath the splenic remnant. *A* and *B* are small intrasplenic and subcapsular cysts.

hilum and over the upper pole of the cyst, and formed about one fifth of the external surface of the specimen. From a maximum thickness of 4 cm., it tapered gradually in all directions to become continuous with the fibrous membrane, which formed the lower part of the wall of the cyst. On the outer aspect of the lower membranous portion there was a scarred area 3 by 2 cm. in diameter. Some remains of adhesions were present on the upper surface of the splenic portion. Along the lower anterior margin of this upper portion several small clear cysts, averaging from 1 to 2 mm. in diameter, were seen projecting out under the splenic capsule. Section of the splenic portion revealed a few minute cysts in the pulp. The contents of these small cysts were serous. The interior of the lower portion



of the specimen was occupied by a single immense oval cyst cavity. The internal lining of the large cyst was perfectly smooth, except beneath the remnant of the spleen, where there were a richly developed trabecularism and ridge formation (fig. 2). These trabeculae appeared as interconnecting beams or arches, leaving both small and large recesses in between. This network was somewhat suggestive of the tendinous cords within the heart. The fluid content of the large cyst removed

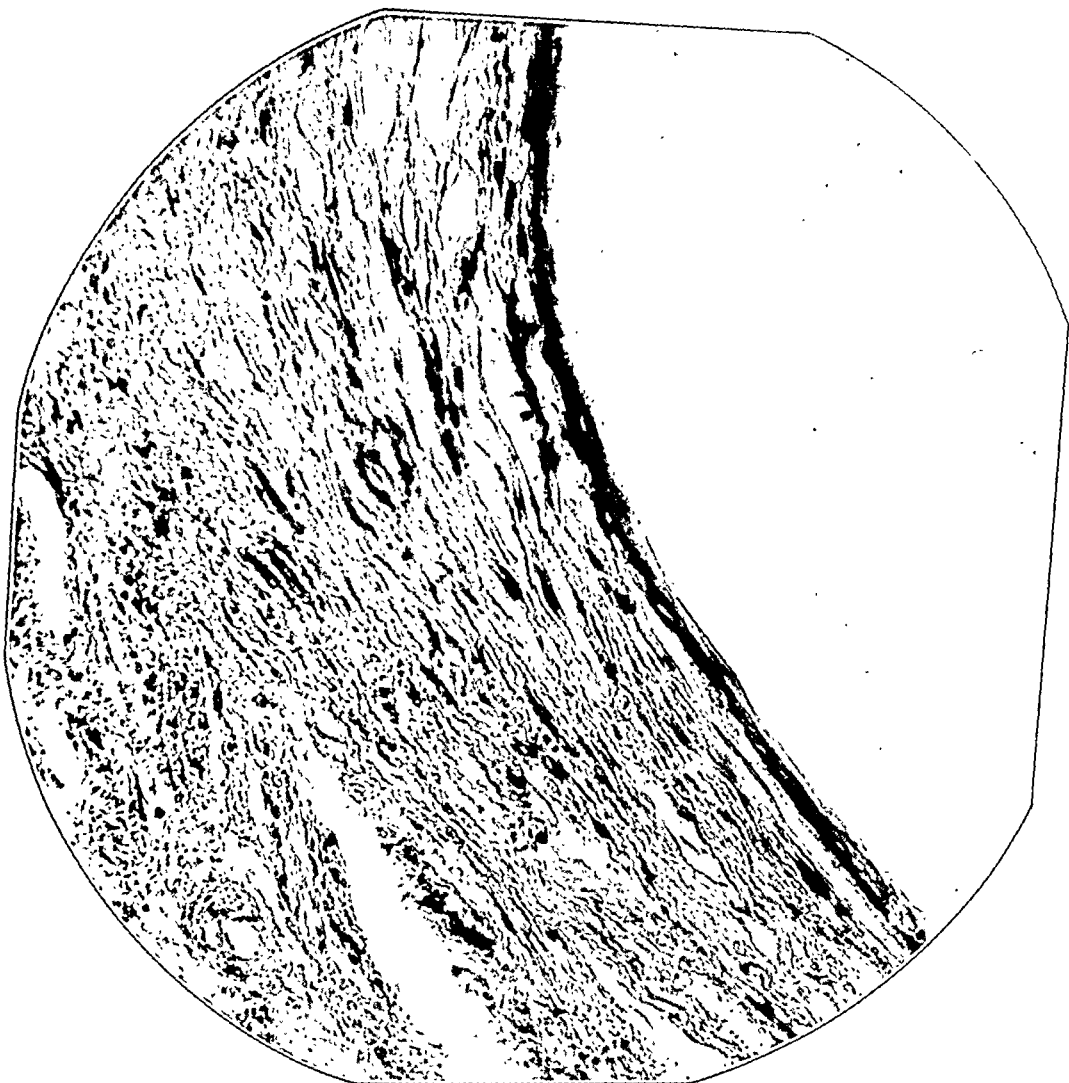


Fig. 3.—High power photomicrograph of section taken from the membranous portion of the wall of the cyst, showing no epithelial lining.

at operation amounted to 1,500 cc. This fluid was moderately thin, brownish and somewhat glistening, and contained fat, cholesterol and blood elements. No echinococci were present. A more complete chemical analysis was not made. Culture of the fluid evacuated resulted in no bacterial growth.

The original sections for microscopic examination immediately after splenectomy were taken only from the membranous portion of the wall of the cyst and showed fibrous connective tissue without any particular lining. It was nine years later,

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during a follow-up examination, that a more complete pathologic examination was made, the result of which is most important in the present report. This microscopic examination was made of sections taken from additional areas of the wall of the cyst and from beneath the splenic remnant. Those taken from the lower portion of the membranous wall of the cyst showed, as originally, nothing of importance. The lining cells were mostly of the fibrous variety, poor in nuclei and sometimes hyalinized (fig. 3).

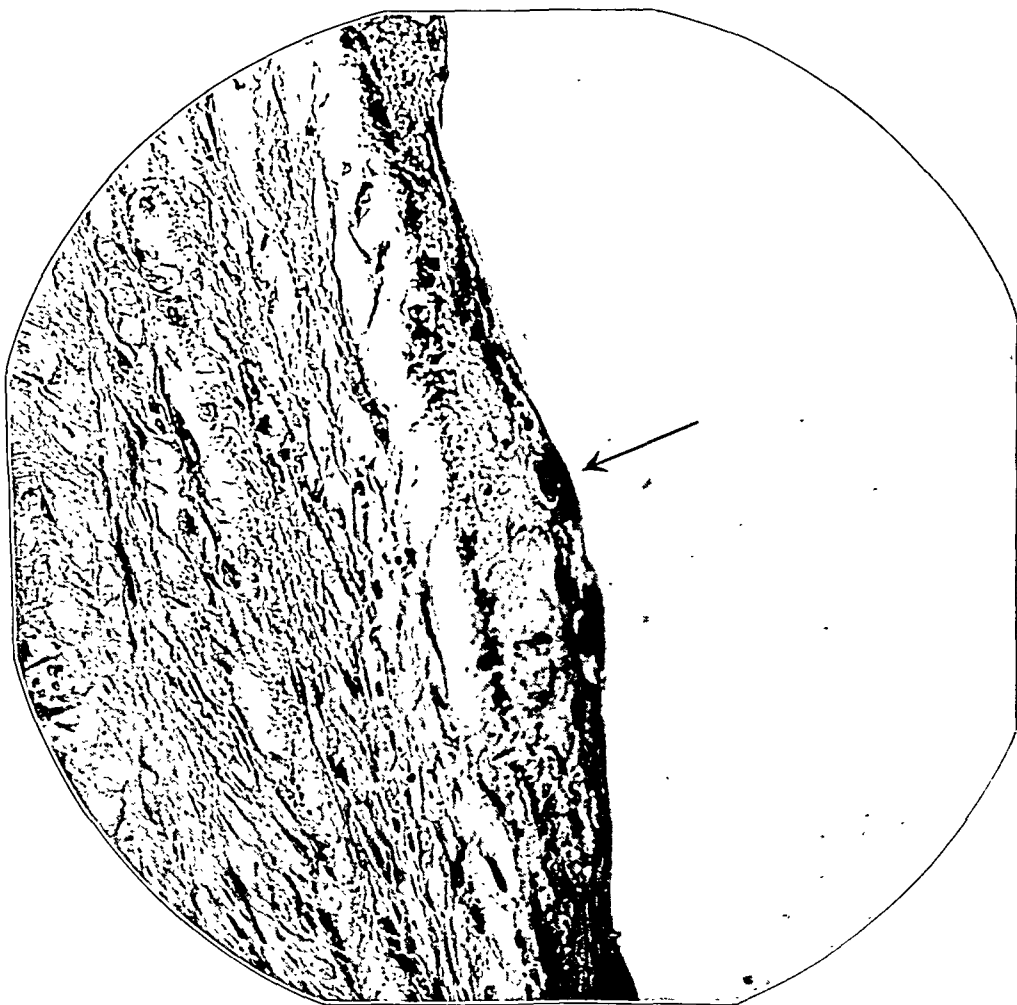


Fig. 4.—High power photomicrograph of a section taken from the membranous portion of the wall of the cyst. The arrow points toward an occasional flattened cell, forming the inner lining of the cyst.

Approaching the subsplenic area (fig. 4), a disconnected simple and gradually a stratified flat cellular lining was encountered next to the lumen of the cyst. In the depths of the niches and recesses this lining became from eight to ten layers thick (fig. 5). On the surface of the lumen there were several layers of flat or spindle-shaped cells, having flattened nuclei. The next three or four layers of cells were polyhedral, and the nuclei were more ovoid. The deepest cell layer was laid

down in a more perpendicular manner and had deep staining rounded nuclei. Under this lining was a loose connective tissue layer which had a different appearance from the connective tissue cells making up the trabecular framework. Definite cornification was not present. In no areas were sweat glands or hair follicles present. The few small cysts in the splenic parenchyma and those just beneath the peritoneum were lined by a more or less continuous layer of flat cells. Certain sections crossed the deep portions of the recesses in such a manner as to make



Fig. 5.—Low power photomicrograph taken from the splenic portion of the wall of the cyst. Note the invagination of the epithelial lining, which is of the stratified pavement type (indicated by arrow).

them appear as islands of many layered pavement cells deposited on a loose connective tissue base (fig. 6). A specimen taken from the splenic parenchyma showed some rather large lymph nodes, some hyaline degeneration and a definite increase in the connective tissue elements (fig. 7).

*Summary.*—In conclusion, it may be stated that this large cyst of the spleen had an inner lining of different degrees of stratification, varying from areas where

a lining was absent or was flat and single-layered to areas that were from five to ten layers thick. The thickest layering was found in the depths between the trabeculae, where it rested on a loose connective membrane. Although this stratified epithelium resembled the epidermis, it was unlike the latter because of the lack of hair follicles, sweat glands, papillary layer and cornification. The splenic remains were normal except for an increase in the connective tissue elements.

This case presents certain things of interest from the clinical, technical, follow-up and pathologic standpoints.

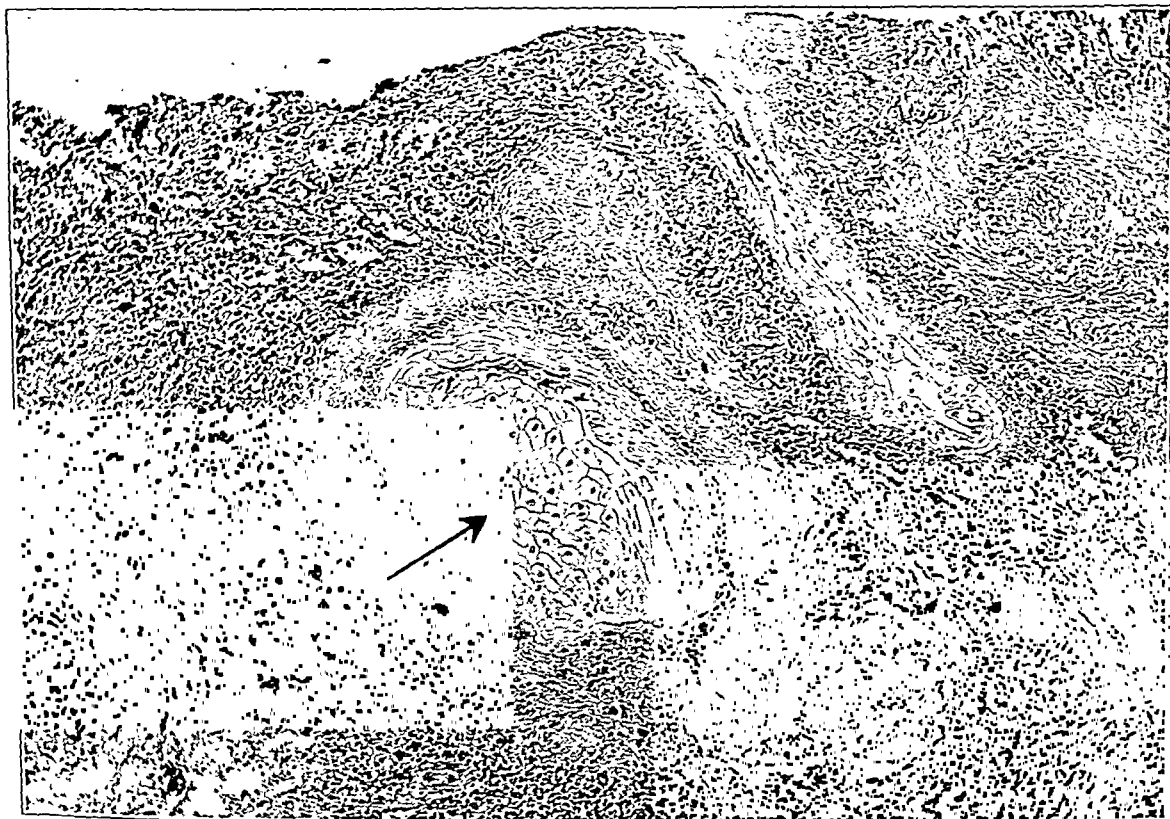


Fig. 6.—High power photomicrograph of the splenic portion of the wall of the cyst, showing a detailed structure of the epithelial lining. The island of stratified pavement epithelium is a cross-section of one of the recesses between the trabeculae. Note the lumen surrounded by many layered pavement cells on a deep staining germinal layer which rests on loose connective tissues (shown by arrow).

#### CLINICAL ASPECTS

From the clinical standpoint, the splenic cyst occurred in a young girl having had slight menstrual irregularities and who also recalled having an injury to the left epigastric region. The relative frequency of splenic cysts in women during the menstrual life is supported by

reports from Hamilton and Boyer<sup>1</sup> (65 per cent) and others. Abdominal injury supposedly resulting in intrasplenic hemorrhagic cysts has often been reported in the literature. On the other hand, according to Frank's<sup>2</sup> statistics, only 22 per cent of seventy-two cases of large splenic cysts gave a history of previous abdominal trauma. Brandberg<sup>3</sup>



Fig. 7.—Low power photomicrograph of the splenic remnant, showing marked increase in connective tissue elements. Note (A) the large connective tissue trabecula.

remarked that "the injury, which need not be particularly severe, is often forgotten when the cysts begin to give symptoms." The pre-

1. Hamilton, C. S., and Boyer, E. H.: Hemorrhagic Cysts of the Spleen, *Ann. Surg.* **73**:58, 1921.
2. Frank, L. W.: Unilocular Cysts of the Spleen, *Ann. Surg.* **75**:360, 1927.
3. Brandberg, R.: Nonparasitic Cysts of the Spleen, *Acta chir. Scandinav.* **63**:346, 1928.

dominant symptoms were mainly mechanical, while the roentgenographic discovery of displaced gastro-intestinal viscera was the most valuable preoperative diagnostic aid. A preliminary aspiration of most of the fluid contents of the cyst rendered splenectomy easy to perform. Contrary to the usual belief, pregnancy may occur in a splenectomized woman, as brought out by the case reported, as well as by the recent article of Mussey and Burkley.<sup>4</sup> These investigators reported thirty-two pregnancies in a series of twenty-three women who previously had had their spleens removed.

#### PATHOLOGIC ASPECTS

It is beyond the scope of this paper to discuss all types of splenic cysts. Suffice to say that they have been well covered in the papers of Fowler,<sup>5</sup> Howald,<sup>6</sup> Pool and Stillman,<sup>7</sup> Lubarsch<sup>8</sup> and others. They are usually classified as: (1) dermoid, (2) nonparasitic and (3) parasitic. Fowler<sup>5</sup> stated that there are two cases of dermoid cysts and ninety of large nonparasitic cysts recorded in the literature. That parasitic cysts are more common is indicated by his estimation of a possible total of one hundred and ninety-one cases reported up to 1894.

Morphologically, nonparasitic cysts can be divided into the large solitary and the small multiple varieties. Based on their possible origin, Fowler suggests that nonparasitic cysts of the spleen be classified as traumatic, inflammatory, degenerative, dilative and neoplastic. Under neoplastic cysts, which include lymphangiomas and hemangiomas, might also be included dermoid cysts, of which only two have been reported (Andral,<sup>9</sup> 1829, and Kumaris,<sup>10</sup> 1915).

To date, reports concerning cysts lined with stratified epidermoid cells are but three in number, so far as I have been able to ascertain. Because they have never been considered together before, I shall at this time briefly review the reports and findings.

1. Schneider<sup>11</sup> (1929) presented before the German Pathological Society a cystic spleen removed from a boy of 14 years. In an exten-

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4. Mussey, R. D., and Burkley, G. G.: Pregnancy Following Splenectomy, *M. Clin. North America* **13**:1455, 1930.

5. Fowler, R. H.: Further Studies of Cysts of the Spleen, *Ann. Surg.* **80**:58, 1924.

6. Howald, R.: Pathogenese der grossen Milzcysten, *Frankfurt. Ztschr. f. Path.* **33**:349, 1926.

7. Pool, E. H., and Stillman, R. G.: Surgery of the Spleen, New York, D. Appleton and Company, 1923, p. 254.

8. Lubarsch, O., in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, p. 1.

9. Andral, G.: *Précis d'anatomie pathologique*, Paris, Gabon, 1829, p. 432.

10. Kumaris: Milzdermoid und Wandermilz, *Arch. f. klin. Chir.* **106**:699, 1915.

11. Schneider, P.: Eine splenomegalische Epidermoidzyste, *Verhandl. d. deutsch. path. Gesellsch.* **24**:280, 1929.

sive analysis of the same case, Dinand<sup>12</sup> (1930) wrote that during the discussion which followed Schneider's presentation, Lubarsch recalled an analogous observation that had not yet been published. In describing the lining wall of the cyst, Schneider observed:

It shows an epithelial lining which at the areas of greatest pressure is uniformly reduced to a single layer of flat cells or is entirely lacking and then is replaced by a fatty granulation tissue. In the still intact areas of growth, however, in the recesses and niches, there is found a many layered pavement epithelium, from five to ten layers high, which sits directly on the splenic trabecular structure without any border or has only a loose skinlike connective tissue layer between it and the trabecular structure. Just occasionally, the epithelium still shows a trace of a germinal layer of dark cells, but for the most part, it consists of light, polyhedral cells with a distinct prickle cell layer; at the upper surface are found flattened cells without cornification. In spite of many examinations, no cutaneous glands or hair follicles could be found.

To explain its origin, Schneider believed that during the development of the spleen in the mesogastrium, some embryonic material lying in the celomic cavity, capable of forming epidermis, was enclosed in the splenic anlage. He denied the possibility of an origin from the spleen itself. He regarded his case as a true epidermoid cyst, and remarked that so far simple epidermoid cysts of the spleen seem not to have been previously reported. Dinand<sup>12</sup> (1930), in discussing the same specimen, assumed either an embryologic displacement or an autochthonous formation from the splenic tissue itself as an explanation of the tumor, and especially of its epithelial lining.

2. Pohle<sup>13</sup> (1929) reported a cystic spleen with similar microscopic findings removed from a 19 year old girl. In his microscopic report, he stated: "It is remarkable to find typical stratified pavement epithelium at one place or another, many times with clearly distinguished intercellular bridges, as the lining of the cyst. Two islands of pavement epithelium situated in a splenic tissue are especially to be noted. Hair follicles and cutaneous glands are not observed anywhere." He concluded that his specimen must most likely be regarded as a congenital dermoid cyst, although its development through metaplastic processes nevertheless appeared possible.

3. Santy<sup>14</sup> (1930), in reporting a splenic cyst removed from a boy of 15 years, described a more or less disconnected inner epithelial lining consisting of two or three layers of pavement epithelium. He noted a close resemblance to the transitional pavement cells of the

12. Dinand, F.: Riesige epitheliale Solitär-cyste der Milz, Arch. f. klin. Chir. 158:485, 1930.

13. Pohle, W.: Ueber Milzcysten, Deutsche Ztschr. f. Chir. 221:211, 1929.

14. Santy, P.: Splénectomie pour un kyste vrai de la rate chez un enfant, Lyon chir. 27:101, 1930.

wolffian bodies. The possible embryoplastic origin from a misplacement of a portion of the wolffian body was also considered by Dinand, who recalled the close position of the anlagen of the spleen and the generative organs in the early stages of embryologic development.

#### COMMENT

In reviewing this group of three cases and my own case from the pathologic standpoint, one is struck by the uniformity of the structural findings. Macroscopically, in each there is found a large cyst of the spleen. The flattened splenic tissue forms a small portion of the wall of the cyst, the remainder being made up of a fibrous connective tissue capsule. The inner wall of the cyst beneath the remnant of the spleen presents numerous tendon-like ridges and trabeculae between which are found recesses and niches. Microscopically, the inner walls of these recesses adjacent to the spleen are lined by stratified, squamous, epidermoid tissue. Between this and the splenic trabecular structure is a loose connective tissue layer. This lining in the recesses resembles the skin, except that cornification, hair follicles, sweat glands and papillae are absent.

To explain the ontogenesis of these tumors, and especially of their epidermoid lining, one may resort to the theory either of embryologic displacement or of autochthonous formation.

*Embryologic Displacement.*—It is possible to have an ectodermal metaplasia in the splenic anlagen. This island of ectodermal tissue may eventually be causative in the formation of a tumor mass and cyst. However, this possibility is not probable in these cases because of the lack of associated structures so commonly seen when an ectodermal metaplasia occurs.

It is also possible that this lining may have its origin in the kidney anlagen capable of producing transitional epithelium. The latter, under certain circumstances, may simulate the stratified squamous epithelium of the skin, including cornification.

*Autochthonous Formation.*—According to this theory, it may be postulated that mesoderm has the ability to form the products of any of the other two primary germinal layers. Thus, for some unexplained reason, the cyst lining may be of the squamous stratified type on the basis of a mesodermal origin. This theory is particularly supported by the work of Fischel.<sup>15</sup> He stated that "the ectoderm and entoderm furnish the organs in the development of which they are concerned, with the epithelial portion only. They, themselves, are unable (with the possible exception of the lens and vitreous humor)

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15. Fischel, A.: *Lehrbuch der Entwicklung des Menschen*, Berlin, Julius Springer, 1929.



to develop an organ in its entirety. On the other hand, an organ may consist entirely of mesodermal tissue, for the mesoderm is able to supply the epithelial element as well as the connective tissue." H. Müller,<sup>16</sup> in his article on the histologic agreement between epithelial degeneration and cancer growth (also reported by Dinand), cited examples of the apparent formation of epidermoid tissue from a germinal tissue layer other than the ectoderm, and concluded that epithelial formation in pathologic processes is not bound by the rule of specificity. Müller presented a photomicrograph of the inner lining of an olecranon bursa which looks much like the photomicrograph seen in Pohle's report and that taken in my case of splenic cyst. This shows many layers of stratified pavement epithelioid cells, a germinal-appearing layer and an underlying loose connective tissue layer which simulates the structure of the epidermis. Here, too, cornification and cutaneous glands are lacking. From these statements, it seems that the development of epidermoid tissue from mesoderm may occur.

#### SUMMARY

1. Epidermoid cysts of the spleen have rarely been described. Only four instances, including the case here presented, plus another unpublished case recalled by Lubarsch, have been noted.

2. So far, all epidermoid cysts of the spleen have been described in young people. Sex seems to play no especial rôle, as two occurred in boys and two in girls.

3. Complete and repeated microscopic examinations of all splenic cysts may add to the number of these epidermoid cysts.

4. Tumor and distress in the splenic region coupled with elimination of other tumors by various clinical methods, especially radioscopic studies, facilitate the correct diagnosis of large splenic cysts.

5. Splenectomy, the most satisfactory treatment in large unilocular cysts, is facilitated by a preliminary evacuation of the contents of the cyst, providing the presence of parasites has been ruled out.

6. A ten year follow-up in the case herewith presented shows no apparent morbidity after splenectomy. One case of normal gestation in a splenectomized woman is added to those previously collected.

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16. Müller, H.: Die histologische Uebereinstimmung zwischen Epithelregeneration und Krebsbildung, *Ztschr. f. Krebsforsch.* **28**:383, 1929.

# INVAGINATION OF THE APPENDICAL MUCOSA PRODUCING SYMPTOMS RESEMBLING APPENDICITIS

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In one week in February, 1931, in the course of routine work, two appendixes were sectioned which showed unusual lesions, and these lesions could be linked up in an interesting way with the clinical data. Therefore, I am presenting the cases in detail.

## REPORT OF CASES

CASE 1.—Mrs. A. S., aged 20, who was first seen in the University of Chicago Clinics, on Dec. 30, 1930, complained that since a delivery five months previously, she had had pain in the lower part of the abdomen and the back almost constantly, accompanied by weakness and apparently unrelated to meals or activity. There was some tenderness low in the midline and in the lower quadrants of the abdomen. On pelvic examination the adnexa seemed to be slightly enlarged and tender. The Wassermann and Kahn tests were negative. The white cells numbered 6,200; the urine was normal. Conservative treatment was advised.

When the patient was seen on Jan. 13, 1931, she had made no improvement, and the masses in the adnexa uteri seemed larger and more tender. She was accordingly admitted to the hospital for further observation on January 29. At that time, there was a white cell count of 8,600, a faint trace of albumin in an alkaline urine and a sedimentation time of 7 mm. per hour. The temperature was as high as 99.4 F. on several occasions. On February 4, a supracervical hysterectomy with a bilateral salpingo-oophorectomy was performed by Dr. M. E. Davis. The distal end of the appendix was injected and slightly bulbous, so an appendectomy was also performed. There was a febrile course, and the patient was discharged on February 18, with a small elevation of daily temperature (from 99.2 to 99.8 F.). When the patient was seen on May 18, for the last time, she had made an excellent recovery and seemed quite normal.

The gross operative specimen showed nearly normal tubes and ovaries, with a slightly thickened appendix. Microscopically, the tubes and ovaries were also almost normal, but the appendix showed unexpected changes. Inside the usual muscular coat was a thin layer of condensed and atrophic lymphoid tissue which, in a few places, showed the typically glandular character of mucosa and submucosa. Intimately apposed to, and within this layer, was an exactly similar one, but the two layers were everywhere distinct and in some places definitely separated. The line of demarcation between them was continuous and regular throughout the whole circumference of the sections studied. Inside the inner glandular layer and outside the outer layer was a loose structure composed of strands of muscularis. The mucosa and submucosa at the center of the section were not involved.

The whole picture suggested an invagination of the mucosa and submucosa of considerable duration sufficiently impacted to produce a pressure atrophy of the surrounding mucosa and submucosa.

The specimen is shown in figure 1.

CASE 2.—Miss N. L., aged 33, was admitted to the hospital on Jan. 2, 1931, on the service of Dr. Walter Palmer. She had been well until four weeks previously, when she began to have sharp pains in the epigastrium and the right upper quadrant of the abdomen, with a dull aching distress in the left lower quadrant and left groin. Her period began three days after the pain, one week prematurely.



Fig. 1.—Low power view of appendix (case 1).

The pain in the left lower quadrant soon subsided, and was followed by pain in the right lower quadrant, which was dull and steady, but became sharp on deep respiration, slight movement or jarring of the bed, and radiated to the right upper quadrant and epigastrium. This was constant for three weeks. She vomited once in the early part of her illness. The distress had no relation to food or bowel movements. At times the weight of the bed clothes was painful. When the patient was admitted she had residual soreness in the lower part of the abdomen, especially in the right lower quadrant. Examination revealed tenderness in the right lower quadrant, especially over McBurney's point, with slight spasm of the right rectus. Pelvic examination showed retroversion of the uterus and resistance in the right

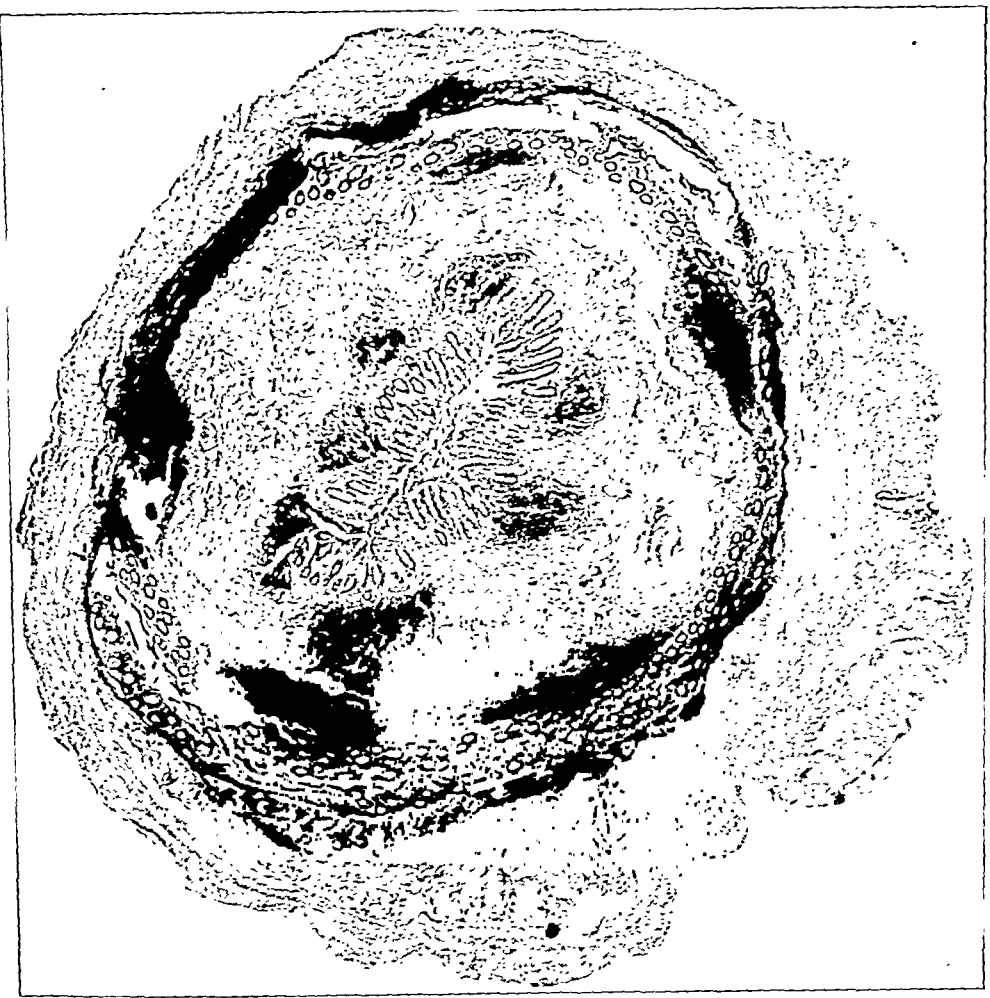


Fig. 2.—Low power view of appendix (case 2).

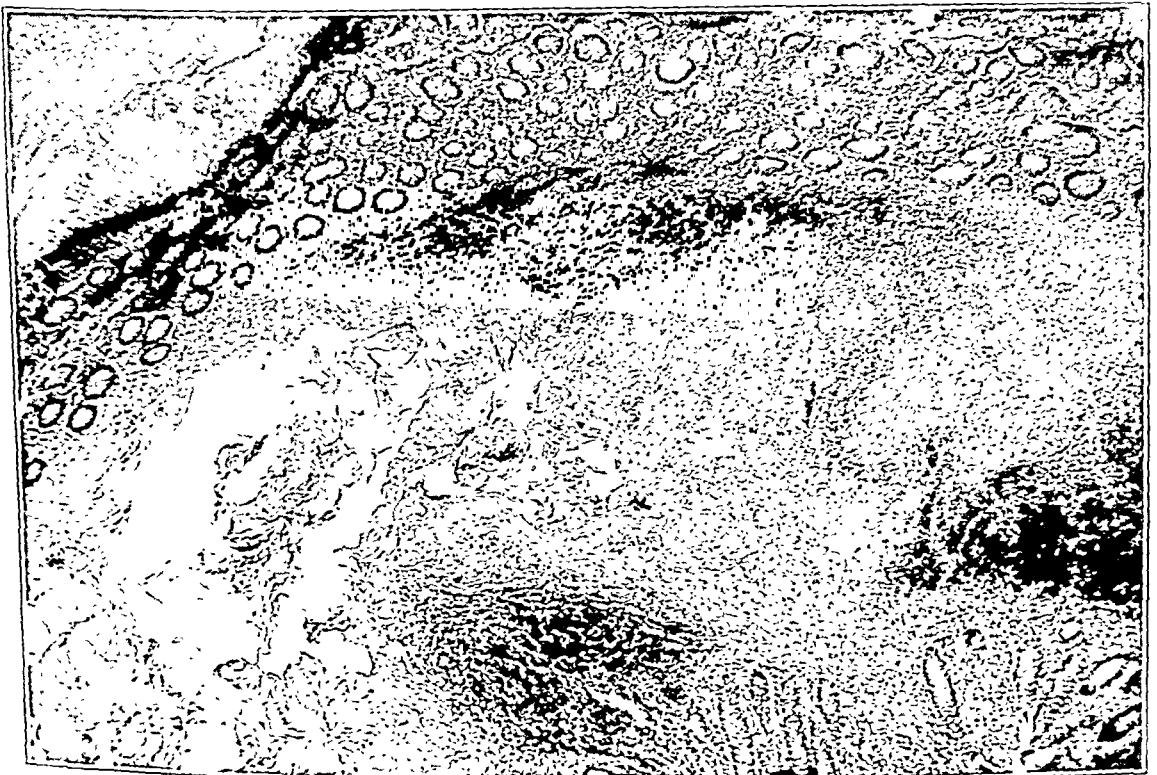


Fig. 3.—High power view of appendix (case 2) showing clearly the two layers of mucosa approximated by the invagination.

adnexa, but the point of maximal abdominal tenderness was definitely above the tubes. There was a leukocyte count of 12,000, of which 64 per cent were polymorphonuclears. The urine was concentrated. Wassermann and Kahn tests were negative. The previous history of disease was unimportant. There had been no previous injuries or operations. The patient refused operation. On January 5, she was discharged as having subsiding acute appendicitis.

The patient had severe epigastric pain on January 18, from 10 p. m. to 1 a. m., without chills or vomiting. The next day there was pain in the lower part of the abdomen, especially in the right lower quadrant, which subsided gradually in the next day or so. However, at 3 a. m. on January 21, the patient was awakened by a sharp stabbing epigastric pain which doubled her up. She vomited an hour later. The pain was somewhat relieved by 6 a. m., but a steady ache remained in

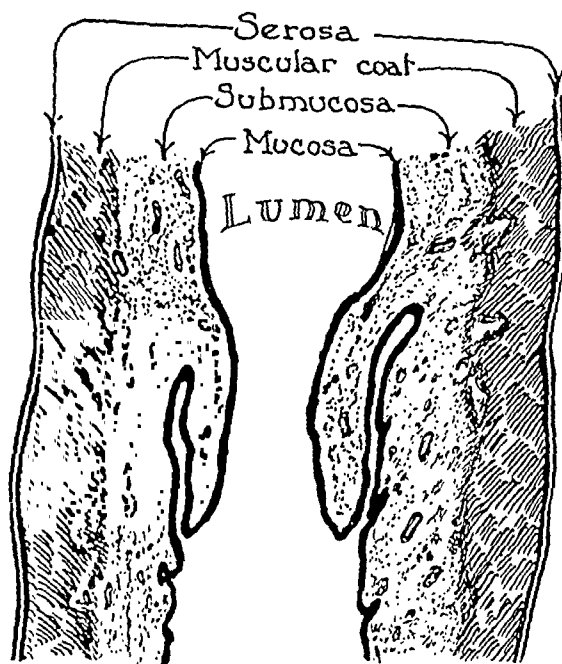


Fig. 4.—Diagrammatic representation of the phenomenon of invagination of the appendical mucosa.

the right lower quadrant. Another brief epigastric attack occurred at 9 a. m. The patient was readmitted to the hospital, and was found to have no fever or abdominal rigidity, but some tenderness at McBurney's point, with definite rebound tenderness. The symptoms rapidly subsided and again a diagnosis of an atypical subsiding acute appendicitis was made. Pelvic examination on January 26 showed the left ovary slightly adherent and enlarged and a right ovarian mass that was tender and adherent. On February 5, these masses had enlarged. At the time of the second admission the white cell count was 17,000, of which 45 per cent were polymorphonuclears and 45 per cent lymphocytes. The urine was normal. On February 6, the sedimentation time was 33 mm. per hour. The following day Dr. F. L. Adair performed a bilateral salpingectomy and removed the appendix. There were filmy adhesions about the tubes and evidences of salpingitis, but the appendix seemed normal. There was an easy postoperative course, and when seen on March 12, the patient was found to be in good health and free from symptoms.

Examination of the operative specimen showed characteristic inflamed tubes slightly thickened and congested. The appendix was slightly thickened, and there were recent fibrinous adhesions about it. Microscopically, there was a typical subacute salpingitis and an interesting appendical condition essentially like that in case 1. However, there was no such definite atrophy of the mucosa and submucosa of the outer ring or of the apposed portions of the invaginated mucosa (figs. 2 and 3).

Figure 4 represents diagrammatically the lesion characteristic of these two cases, as seen on sagittal section taken through the appendix.

#### COMMENT

The literature contains many reports of complete or partial intussusception of the appendix. In 1922, Szenes<sup>1</sup> collected the literature up to that time. He found only one case of intussusception of the appendix into itself in which there was no cecal involvement as well, viz., the case of Kuss and Guimbellot. However, he cited Rolleston's<sup>2</sup> case and Schmidt's two cases, in all three of which there was a pseudo-invagination and incomplete involvement of the appendix. In a later review, Huddy<sup>3</sup> remarked that Szenes apparently overlooked the cases of Treves,<sup>4</sup> Johnson,<sup>5</sup> MacClennan's<sup>6</sup> two cases, and an unpublished specimen in the museum of the Royal College of Surgeons obtained by H. B. Robinson.<sup>7</sup> Szenes also overlooked several cases cited by Battle and Corner<sup>8</sup> in their good review of 1911, namely, Bishop,<sup>9</sup> Furniss<sup>10</sup> and Grisel.<sup>11</sup> Huddy adds to the list of the cases published a number appearing since Szenes' paper, namely, those of Evans,<sup>12</sup> Hipsley,<sup>13</sup> Brin and Fruchaud-Brin,<sup>14</sup> Huese,<sup>15</sup> Trince,<sup>16</sup> McIntosh,<sup>17</sup> and

1. Szenes, A.: *Arch. f. klin. Chir.* **119**:88, 1922.

2. Rolleston, H.: *Edinburgh M. J.* **4**:21, 1898.

3. Huddy, G. P. B.: *Brit. J. Surg.* **14**:580, 1927.

4. Treves, Frederick: *Intestinal Obstruction*, Philadelphia, H. C. Lea, 1884, p. 172.

5. Johnson, G.: *Brit. J. Surg.* **3**:564, 1916.

6. MacClennan: *Clin. J.* **48**:78, 1919.

7. Robinson, H. B., cited in Battle, W. H., and Corner, E. M.: *Surgery of Diseases of the Appendix*, London, A. Constable & Company, 1910, p. 193.

8. Battle and Corner (footnote 7).

9. Bishop: *Chironian* **10**:81, 1902, cited by Battle and Corner.

10. Furniss: *Am. J. Obst.* **58**:307, 1908.

11. Grisel, P.: *Maladies du tube digestif*, Paris, 1908, vol. 2, p. 333; cited by Battle and Corner.

12. Evans, A.: *Brit. J. Surg.* **9**:565 (April) 1922.

13. Hipsley, P. L.: *M. J. Australia* **2**:65 (July 15) 1922.

14. Brin and Fruchaud-Brin: *Bull. et mém. Soc. anat. de Paris* **93**:243, 1923.

15. Huese, J. F. O.: *Nederl. tijdschr. v. geneesk.* **1**:2393, 1923; cited by Huddy (footnote 3).

16. Trince: *Riv. di clin. pediat.* **21**:10, 1923; cited by Huddy.

17. McIntosh, R. D.: *M. J. Australia* **1**:216 (Feb. 25) 1922.

doCouto.<sup>18</sup> I should like to add those of Bobrik,<sup>19</sup> Whitrow,<sup>20</sup> Horn,<sup>21</sup> Hamilton,<sup>22</sup> MacDermott,<sup>23</sup> and the unpublished cases of Myles and O'Connor which MacDermott mentioned to complete the list of publications to date.

However, no case so far reported seems to present quite the same conditions as those found in the two cases reported in this paper. It is true that Rolleston noted that in his case the mucosa alone was involved in the intussusceptum, and that except for the dense adhesions, from the outside nothing abnormal would be suspected. The lesion was discovered only at autopsy when the cecum was opened; the invaginated portion was only about  $\frac{1}{2}$  inch long (12 mm.). In Schmidt's two cases there were appendical cysts, and the appendix seemed normal externally. Watson's<sup>24</sup> case was very similar to Rolleston's, and led to the formation of a long intussusceptum.

Appendical valves are not described in the literature, so far as I know. The picture presented by our specimens would not coincide even with such an explanation, however. It is true that the segment of appendix containing the invaginated mucosa was only a few millimeters long, as was found by taking serial sections of the involved portion. Intestinal valves rarely extend around the whole periphery of the bowel, but tend to be crescentic. The sections of our specimens all showed, however, a symmetrical relation of the containing and contained portions of the appendix, and Dr. F. L. Adair commented on the importance of this feature in diagnosis. Prof. H. G. Wells remarked on the pressure atrophy of the mucosa and submucosa of the outer ring, which was seen best in case 1, in which the impression of an invaginated portion sufficiently large to exert considerable pressure for some time was obtained. It was suggested by Dr. R. S. Jason and later by Prof. H. G. Wells that this was a sort of intussusception of the appendical mucosa. The slides have been studied by Dr. F. L. Adair, Dr. R. S. Jason and Dr. H. G. Wells, and all agreed on the diagnosis.

Christeller and Mayer (see Rössle) and Rössle<sup>25</sup> have observed a few cases in which portions of mucosa had grown down into the muscularis along fistulous tracts or to line abscesses in the wall. Rössle

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18. doCouto, J.-E.: *Etude sur l'invagination de l'appendice*, Thèse de Paris, 1925; cited by Huddy.

19. Bobrik, N.: *Zentralbl. f. Chir.* **41**:518 (March 2) 1929.

20. Whitrow, F.: *Brit. M. J.* **2**:181 (Aug. 2) 1930.

21. Horn, H. W.: *Ann. Surg.* **81**:1002 (May) 1925.

22. Hamilton, T.: *M. J. Australia* **1**:408 (April 4) 1931.

23. MacDermott, E. N.: *Brit. M. J.* **1**:793 (May 9) 1931.

24. Watson, J. H.: *Lancet* **2**:942, 1911.

25. Rössle, R.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **42**:143, 1930.

shows a fine picture of such a specimen. A moment's consideration will show how different is the picture presented by the appendixes in the present cases.

It is to be noted that the muscularis in the deep submucosa in both these appendixes was very loose and almost fragmented for a considerable distance on each side beyond the actual site of the telescoping phenomenon. This allowed easy motion of the mucous layer on the adjacent wall. No inflammatory process ensued in these appendixes. The filmy adhesions seen in case 2 were entirely of pelvic origin. Microscopic examination did not reveal periappendicitis or appendicitis. The symptoms developed in each case from a lesion that was entirely mechanical. The observations were quite accidental. Most normal-appearing appendixes are casually treated everywhere, and one cross-section is usually thought sufficient to demonstrate the presence or absence of inflammatory involvement. However, the importance of longitudinal sections or at least numerous cross-sections of every appendix is clearly demonstrated by the aforementioned observations.

The symptoms in case 2 were definitely appendical, of four weeks' duration, and were characterized by at least two exacerbations sufficiently marked to warrant admission to the hospital for appendicitis. The classic phenomena were present to some degree, but there was no fever. The vomiting was slight; the leukocytosis, especially of polymorphonuclears, was slight, and the symptoms were unduly prolonged at a subacute level. There was no marked rigidity and no modification of bowel or urinary habit. The whole picture in this case, of course, was complicated by the adjacent active salpingitis, but I think that the major portion of the symptomatology was due to appendical factors. In case 1 the patient showed abdominal distress and pelvic signs of a more indefinite character, but the only significant finding was the appendical one, and most of the patient's symptoms must be ascribed to the appendix.

The occurrence of repeated appendical attacks, none of which is definitely an "acute appendicitis," with its characteristic low fever, vomiting, leukocytosis, temporary constipation, or urinary frequency, marked right rectus rigidity and localized tenderness should suggest the possibility of an appendical lesion of a type not hitherto suspected. MacDermott noted that slight intussusceptions may produce vomiting late or early, with no rise in temperature, pulse or increase in abdominal rigidity until the appendix becomes inflamed. Many a surgeon has felt slightly ashamed to operate for "appendicitis" of this type, even if it produced prolonged and marked discomfort such as was found in our two cases; he has been more regretful when no gross or microscopic changes in the suspected organ were visible. In such cases more cross-sections or longitudinal sections might have revealed just such a lesion



as I am discussing. MacDermott wonders, "if recurrent intussusception, spontaneously reduced, may not frequently be the real lesion in many cases which, though presenting no obvious lesions at laparotomy, are relieved of symptoms by appendectomy." He cited Alvarez' films of intestinal movements which show intussusceptions occurring and reducing themselves spontaneously. He mentioned an unpublished observation of Myles of such an invagination of the appendix into the cecum, occurring spontaneously and reducing itself with regular rhythm in a patient on whom he was operating for cecal hernia. He ascribes the beneficial effects of atropine in some cases of "chronic appendicitis" to similar processes.

As regards etiology, it is now generally accepted that the appendix is a mobile organ with peristaltic activity. Movement of the internal layers may occur apparently even when the serous coat is fixed by adhesions, as in Rolleston's case and our case 2. Bohême and Reny<sup>26</sup> remarked that at the appendix the colon's antiperistalsis meets the ileal and appendicular peristalsis so that telescoping at this site readily develops. At the meeting place of these waves of peristalsis and antiperistalsis adjacent portions of virtually the same organ are synchronously relaxed and contracted, a situation which is ideal for telescoping phenomena. If there is a mild inflammation adjacent to the appendix it is probably stimulated to increased activity. It is well known that the ileocecal-appendicular region is the focus from which most intussusceptions of the bowel begin. If the distal end of the appendix is adherent, the waves from the bowel running into it tend to force it into the adjacent distensible cecal cavity or into its own relatively large base. The factors that influence intussusception of the organ, as a whole, also have the same effect on its component layers, especially when those layers are loosely bound together, as in the cases which I am reporting. There is no good reason why the factors necessary to produce such lesions should not often arise, and I suspect that they are not uncommon.<sup>27</sup>

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26. Bohême, P., and Reny, P.: *Rev. de chir.* 47:287, 1929.

27. Dr. F. L. Adair and Dr. M. E. Davis gave me permission to publish the two cases described.

# OSTEOMYELITIS OF THE SKULL

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## INTRODUCTION

The present communication is concerned with osteomyelitis of the flat and irregular bones of the skull exclusive of the maxilla. The principles of the pathogenesis of acute osteomyelitis in general will be incorporated in this paper as they apply to osteomyelitis of the skull, and any differences from the usual manifestations found in the long or other irregular bones of the body will be found to occur as a result of the essential structure of the cranial bones. Any extraordinary phenomena associated with osteomyelitis of the skull that occur in a large clinical group result from its origin in the neighboring nasal accessory sinuses or in the otologic apparatus, and are associated mainly with the development of intracranial secondary complications which commonly dominate the clinical picture.

In this communication I shall consider only those cases of acute osteomyelitis of the skull that are caused by the common pyogenic organisms—staphylococci, streptococci, pneumococci, etc. I shall not include any cases due to infection by the tubercle bacillus. *Spirochaeta pallida* or by *Actinomyces*.

Cases of acute osteomyelitis of the skull frequently last a long time and assume the characteristics of a chronic infection; such cases are included, as one should consider them to be long drawn out cases of acute osteomyelitis. No other variety of chronic pathologic process of the bones of the skull is, however, included in this discussion; neither are the forms of necrosis of the skull due to phosphorus or other similar forms of poisoning, nor the group of peculiar cases marked pathologically by various forms of hypertrophic osteitis included. Cases of acute and chronic bone change associated with certain forms of essential blood disease are, of course, completely separated from the subject.

## HISTORICAL

Although osteomyelitis of the skull undoubtedly must have occurred frequently prior to the eighteenth century as a consequence of civil and military injuries about the head, involving the skull, the association of the injury and the consequent clinical manifestations with infection of the bone tissue of the skull was not suspected or recognized until long

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From the Mount Sinai Hospital.

after knowledge was prevalent concerning similar associations in the long bones. The skull conditions were first described by Pott<sup>1</sup> in 1768 under the name of bone contusion. He believed that these lesions were always caused only by contusion. He assumed that in every severe contusion detachment of the dura mater is caused by an extradural hematoma; that the hematoma irritates the dura, and that the irritation increases and causes suppurative inflammation. In 1859, Chassaignac<sup>2</sup> suspected that the condition was a true bone disease, but this remained only a theory until it was proved by Lannelongue<sup>3</sup> in 1879 that cranial para-osseous abscesses were due to disease of the bone itself. It was then still a hundred years before the real nature of the disease was known, and the route of infection was not discovered until even later than that. In 1882, Fischer<sup>4</sup> wrote of apparently spontaneous inflammation of the skull that it was probably caused by progressive suppuration in the neighboring tissues. In 1889, cases of cranial osteomyelitis having an origin in the nasal accessory sinuses were described by Luc<sup>5</sup> and Tilley.<sup>6</sup> Later cases were reported in which there was an otologic origin. Finally, as bacteriologic knowledge increased, it began to be recognized that osteomyelitis of the skull could also be hematogenous or metastatic, and the first mention of this etiologic relationship is made by von Bergmann<sup>7</sup> in his "Handbook of Practical Surgery" in 1900.

#### FREQUENCY

In the modern period, and especially in the antiseptic and aseptic periods, cases of osteomyelitis of the skull following injury have become scarcer and scarcer, so that now it would be difficult, I imagine, for any one to gather together a hundred cases of traumatic osteomyelitis of the skull from his own experience, as Fischer did in 1882. On the other hand, with increasing knowledge, cases due to other causes, especially to nasal accessory sinus disease, have seemingly increased in number

1. Pott, P.: *Observations on the Nature and Consequences of Those Injuries to Which the Head is Liable from External Violence*, London, 1768.

2. Chassaignac (1859), quoted by Kallenbach: *Beitr. z. klin. Chir.* **128**:725, 1923.

3. Lannelongue, O.-M.: *De l'ostéomyélite aiguë pendant la croissance*, Paris, Asselin & Cie, 1879.

4. Fischer, H.: *Deutsche Ztschr. f. Chir.* **56**:100, 1900.

5. Luc: (a) *Arch. de laryng. et rhinol.* **12**:280, 1899; (b) *J. Laryng.* **14**:473, 1899; (c) *Brit. M. J.* **2**:993, 1899; (d) *Ann. d. mal. de l'oreille, du larynx* **28**:497 (Dec.) 1902.

6. Tilley, H.: *Lancet*, 1900, vol. 2; *Tr. Lon. Laryng. Soc.*, March, 1904; *Brit. M. J.* **2**:7, 1917; *J. Laryng. & Otol.* **38**:78 (Feb.) 1923.

7. von Bergmann, A.: *Handbuch der praktische Chirurgie*, 1879; *St. Peters. med. Wchnschr.* **37**:38 and 389, 1884.

because the medical profession has learned to look for them and to recognize the etiologic relationship, and because attention is forcibly called to the lesion by the dramatically dominating secondary intracranial complications which take place.

One reason why nontraumatic forms of osteomyelitis of the skull were not recognized for such a long time is that they are so rare. Scheinziss<sup>8</sup> found that among 1,782 cases of osteomyelitis of the long and flat bones there were only ten of osteomyelitis of the skull; in Kiel there were four cases among 400, and in Kallenbach's<sup>9</sup> clinic, three among 620. According to Trendel,<sup>10</sup> only five cases have been seen in the Tübingen clinic in fifty years; in Kiel four cases have been seen in twelve years, and in Poppert's clinic in Giesen, three cases in fourteen years.

According to the records at Mount Sinai Hospital for the period from 1924 to 1931, there were 331 cases of acute osteomyelitis of all the bones of the body; among these there are records of seventeen cases of osteomyelitis of the skull—a percentage of 5.

In my own experience I have seen osteomyelitis of the skull as a hematogenous infection in one case, as an operative infection in one case, as a complication of nasal accessory sinus disease in two cases, and several traumatic cases—all of this in a space of twenty years. I believe this to be an average experience for a general surgeon.

According to Trendel,<sup>10</sup> who collated the statistics of Haaga<sup>11</sup> and Fröhner,<sup>12</sup> osteomyelitis in the flat bones occurs in the relationship of 1:6.6 to osteomyelitis in the long bones, and osteomyelitis of the skull occurs in about 3 per cent of the cases in the flat bones.

Taking the matter all in all, the number of cases of cranial osteomyelitis that are encountered at the present time in hospital and private practice are small and, possibly, will continue to grow smaller owing to greater knowledge of prophylaxis, especially in the care of the provocative origins in the nasal accessory sinuses and in the otologic apparatus.

#### CRANIAL AREAS INVOLVED

The commonest location for the development of an osteomyelitis of the skull is the frontal and the parietotemporal regions. This is in correspondence with the common locations for the reception of head injuries, and because of the close contiguity to the frontal and other nasal accessory sinuses and to the auditory apparatus—the commonest sources of an extension form of osteomyelitis of the skull.

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8. Scheinziss, M. W., quoted by Kallenbach (footnote 9).

9. Kallenbach: Beitr. z. klin. Chir. **128**:725, 1923.

10. Trendel: Beitr. z. klin. Chir. **41**:607, 1904.

11. Haaga, P.: Beitr. z. klin. Chir. **5**:49, 1889-1890.

12. Fröhner, E.: Beitr. z. klin. Chir. **5**:79, 1889-1890.

In the cases at Mount Sinai Hospital the areas in which the osteomyelitis was distributed were as follows:

Frontal bone	6 cases
Frontal and parietal bones	2 cases
Frontal and ethmoid bones	2 cases
Temporal bone	1 case
Temporal bone and zygoma	1 case
Parietal bone	1 case
Sphenoid bone	3 cases
Sphenoid and ethmoid bones	1 case
Petrous pyramid	1 case
Zygoma	1 case

In Kallenbach's <sup>a</sup> series, the distribution was as follows:

Frontal bone	15 times
Frontal and parietal	1 time
Temporal	8 times
Parietal	5 times
Occipital	3 times
Sphenoid	
Frontal and temporal	2 times
Frontal, temporal, parietal and occipital	1 time

#### AGE

In consequence of the protean character of the causative origins of cases of osteomyelitis of the skull, the prevalent ages at which the cases seem to develop are in conformity with the ages for which these origins, trauma, nasal accessory sinus disease, etc., seem to have some special predilection. Traumatic cases are likely to occur at any time; extension cases, especially those of nasal sinus origin, are also likely to occur at any age, but develop usually in young or middle adult life; hematogenous cases follow the prevalence of these acute general infections with localizations in the bones and are apt to occur in childhood, at puberty or young adolescence. In the cases at Mount Sinai Hospital the age distribution was as follows:

Up to 10 years	5 cases
11 to 20 years	4 cases
21 to 30 years	1 case
31 to 40 years	1 case
41 to 50 years	5 cases
51 to 60 years	2 cases
60 to 70 years	1 case

#### PATHOLOGIC PROCESS IN OSTEOMYELITIS OF THE SKULL

*Gross Pathology.*—Mild cases affecting the external table of the skull correspond in their pathologic process to osteomyelitis of the long

bones limited to a relatively small area of the cortex. The circulation becomes shut off from a number of vessels in the external table and, depending on their number and on the extent of collateral circulation, a segment of bone is sequestered and discarded. The sequestered parts take the form of small flakes of bones, or thin segments of irregular shape. The suppuration that accompanies this gathers between the outer table and the pericranium and corresponds to a subperiosteal abscess of the long bones.

Mild cases affecting the internal table correspond in their particulars to those of the external table.

In more severe cases of osteomyelitis of the skull involving both the external and internal tables of the skull, and in the diffuse and in the spreading varieties, the pathologic process is more extensive, and a dominant place is taken by the diploic network of veins.<sup>13</sup> The description that follows applies generally to all types of osteomyelitis of the skull without reference to the etiologic cause or condition; it is, however, particularly applicable to cases that result from disease in the nasal accessory sinuses. The pathologic anatomic appearances of the lesions vary with the stage of the disease. In the early stages, the bone presents no abnormalities evident to the naked eye, although during life the diploe might perhaps show some congestion. In the next stage, the diploe on section is seen to be markedly hyperemic and to be interspersed here and there with drops of pus. This is followed by the conversion of the medullary tissue of the diploe into granulation tissue bathed in pus, which, on section of the bone, exudes copiously from the cut surfaces. Thrombosed veins may be seen occupying the diploe. In the third stage, the purulent secretion, finding its way to the outer and inner surfaces of the bony cranium by the vascular channels or through minute openings formed by the resorption of bone tissue, collects to form abscesses between the bone and the pericranium on the one hand, and between the bone and the dura on the other—the para-osseous abscesses.

In the external variety of abscesses, the pericranium, raised off the surface by the accumulation, quickly undergoes dissolution, so that the collection of pus comes to lie in the subcutaneous tissues of the scalp. No delimiting abscess wall is formed, but the pericranial abscesses are, nevertheless, when they are multiple, quite discrete and separate from each other. These are the doughy or puffy swellings of the scalp, which form a striking clinical feature of the disease.

The dura shows little or no tendency to break down for considerable periods of time. Larger and smaller collections of pus gather in the extradural space which, when sufficiently large, may give rise to com-

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13. The anatomy of the diploic veins is described subsequently. See section on "Pathogenesis."

pression of the intracranial contents. The bony (external) wall of the abscess remains bare, but the dural (internal) surface becomes covered with shaggy granulations. Fine adhesions are usually demonstrable between the deep surface of the dura and the underlying arachnoid.

The fourth stage of the lesion is marked by more or less widespread destruction of the tables of the skull, the external usually giving way before the harder vitreous. By this time more or less extensive areas



Fig. 1.—Low power picture of a section of a skull the seat of an osteomyelitis of the diffuse type, showing the dead bone and the suppurating diploic spaces. (Figures 1, 2 and 3, courtesy of Dr. Klemperer.)

have undergone necrosis. Sequestration occurs either in large masses, sometimes of characteristic shape, or in small flaky segments. An eroded or wormeaten appearance of the outer table of the skull has given rise to such descriptive terms as "lace-work" (Tilley<sup>6</sup>), or as if it had been "corroded with acid" (Luc<sup>5</sup>).

During the active stages of the development of an osteomyelitis of the skull of this type, new formation of bone, which occurs with such

rapidity and exuberance in osteomyelitis of the long bones, either does not appear at all, or is scarcely perceptible. On microscopic examination, some little attempt at regeneration may be visible, but it is entirely overshadowed by the processes of destruction. Indeed, in this respect, as in many others, the reactive efforts of the tissues seem to be feeble and incompetent. In favorable cases, in which healing and cicatrization become definitely established, however, the gaps made in the skull by the spontaneous, or operatively produced, loss of tissue are almost filled up again by the formation of new bone.



Fig. 2.—Higher power picture of one of the diploic spaces, showing the dilated diploic veins and the suppurative inflammation that is present. Osteoclastic destruction of the bone is visible at the periphery of the space;  $\times 140$ .

*Microscopic Pathology.*—Microscopically, early specimens show that the first changes consist in an invasion of the bone spaces by micro-organisms, with round cell infiltration of the medullary spaces, the walls of which, at this period, are still quite smooth, or are only just beginning to show some signs of lacunar absorption. The diploe is hyperemic and congested. Its consistency is decreased, and it contains small fungous growths and droplets of pus. It soon becomes grayish and contains sequestrums. They are generally numerous and small and may remain in the bone for a more or less long time or may be eliminated. The alterations of the bone are especially seen on the external table.



The later changes, which may be regarded as secondary to the necrosis of the bone, consist in the replacement of the bone marrow by granulation tissue, with absorption, erosion and finally disappearance of the bony trabeculae of the diploe. The outer and inner tables withstand the eroding action till a still later period, so that extensive sheets of granulation tissue develop between the still intact, though lifeless, tables. The blood vessels contain thrombi more or less infiltrated with pus cells, and signs of perivascular inflammation accompany the thrombosis when it progresses in advance of the general bone disease.



Fig. 3.—Higher power picture of the periphery of one of the diploic spaces, showing in greater detail the osteoclastic destruction of the cranial bone;  $\times 180$ .

The lesions are seldom confined to the bones, but the integuments become inflamed and infiltrated with pus. A case is described in the literature by Smith<sup>14</sup> in which a segment of skull with its covering of scalp exfoliated in one piece.

The dura mater is always affected and becomes thickened and granular throughout the entire extent of the lesion of the bones. If the lesions do not evolve too rapidly, adhesions are formed in the arachnoid and the brain is protected against encephalitis. But once the natural resistance is overcome, the infection may reach the pia mater and cause

14. Smith: Tr. Clin. Soc. London 3:163, 1870.

any of the varieties of meningitis, or the suppuration may extend to the brain and the large cerebral sinuses. The latter seems to be the most common complication.

In cases in which general blood infection occurs, the viscera show lesions of a general infection (pyemia). The liver may be increased in size and may show amyloid degeneration. The spleen becomes hypertrophied. The lungs show nodules of hepatization and bronchopneumonia.

### PATHOGENESIS

According to the pathogenesis involved, cases of osteomyelitis of the skull can be divided into three groups: primary, hematogenous and extension cases.

#### PRIMARY CASES

In common with the usual forms of osteomyelitis of the long bones, and to a much less extent, osteomyelitis of the skull is at the present time a comparatively rare phenomenon as a primary disease of the skull, because it can result only as a consequence of trauma.

*Traumatic Cranial Osteomyelitis.*—In 1923, Kallenbach could gather from his own experience only five cases of osteomyelitis of the skull which followed trauma. In one case a blow resulted in a wound which, having apparently healed, opened some days later and discharged; bare bone was felt. In another patient the scalp wound suppurated, and involvement of the bone was established on the twelfth day. In the other three cases it is not definitely established that the mechanism was a primary infection of the bone.

My own experience includes one case in which the trauma was an operative one—an osteoplastic craniotomy; except for this case, the total of this type that I have seen does not number more than two or three in an experience of twenty years.

In accordance with the manner of application of the trauma, and because of peculiarities essential to the latter, one distinguishes the following forms: civil injuries, i. e., falls, blows, etc.; gunshot injuries, including civil and military practice; and osteomyelitis following operative manipulation, i. e., craniotomy of various kinds, etc.

Gunshot wounds form a class by themselves and will not be discussed in this communication. The essential differences between gunshot wounds in civil life and during a military emergency are threefold: (a) the depleted and exhausted condition of troops on the battle line, (b) the enormous increase in environmental contamination (usually of a fecal nature) incident to active warfare in the field, (c) the large size and complexity of the wounds—almost always complicated with intracranial injury, the dominance of which makes for naught any infection of the skull bone—and (d) the enormous mortality. It was learned during the last war that the best prophylaxis is an efficient débridement.

Operative infection occurs so rarely nowadays as to be of negligible importance. The usual course of affairs is illustrated by the following personal experience:

In a patient on whom I did an osteoplastic craniotomy, a local infection developed in the wound and was discovered at the first dressing. A very protracted healing followed, which terminated only after a small sequestrum was discharged from the sinus. (Private records.)

In this communication the main concern is the ordinary forms of civil injury to the head. The correct conception of the pathogenic relationship between a head injury and any resultant osteomyelitis of the skull may be one of two: (1) as primary infection and (2) as a hematogenous infection of the skull.<sup>15</sup>

1. Osteomyelitis may be a primary infection, the result of the direct introduction of organisms into the bone tissue. In such cases, primary osteomyelitis of the skull can develop only when a trauma results in an open wound leading down to the skull, in which the solution of continuity of the tissues extends partially into, or completely through, the thickness of the skull.

Contamination of the wound is the rule; but in modern times the establishment of an infection in the bone tissue and its secondary effects (necrosis due to vascular shutoff) is very rare. This is altogether due to proper methods for débridement of the wounds. In the unfortunate case in which osteomyelitis does develop, the area of bone involved depends on the extent to which the thrombophlebitis becomes established; usually this is relatively circumscribed unless the infection reaches into the diploic veins and a thrombophlebitis becomes established in the latter network. It is a remarkable fact that this should happen on such few occasions.

A particularly interesting case is the following in which the infection took place in the apparent absence of any infection of the nasal accessory sinuses; this was an operative infection. (Unless otherwise noted, the hospital cases are from Dr. Elsberg's service.)

A man, aged 44, had an old fracture of the nasal bone; four months before admission, a plastic operation was performed for the correction of this defect, following which there developed severe pain about the right eye and the right side of the nose and a swelling about the right eye; the latter was incised and drained. Three weeks later another incision was made over the glabella. Three weeks after this, incision and drainage over the right frontal region was performed. The patient had had severe frontal headaches ever since his first operation three months previously. All the wounds continued to drain.

Neurologic examination on admission gave negative results. Intranasal examination revealed a left suppurative ethmoiditis and obliteration of the right frontal sinus due to the old operation and a badly deviated right septum, and a

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15. The second alternative is discussed in the section on "Hematogenous Cases."

scarred right ethmoid area. Roentgen examination of the skull revealed osteomyelitis of the frontal bone. Operation was performed, sequestrums removed, and the dura exposed but not entered. The patient continued thereafter to have severe temporal headaches without any positive neurologic findings. Febrile and afebrile periods alternated. A revision of his former wound was done; further sequestrums were removed, and a small abscess over the occiput was incised and drained. The patient nevertheless continued to become progressively worse. Subsequent roentgen examinations showed an extensive osteomyelitis. An exploratory craniotomy was then performed, but no abscess was found. After two weeks more of this septic course, during which time the patient deteriorated more mentally and physically, a last attempt was made to find some intracranial focus. During this exploration the entire frontal bone, on both sides, was found soft, necrotic and fragmented. Aspiration of the brain substance gave negative results. The patient was delirious in the morning of the operation, stuporous later in the day, and died shortly thereafter. Permission for postmortem examination was not obtained. The infection was due to *Staphylococcus aureus*.

It appears from the literature that the types of operative manipulations done in the presence of nasal and nasal accessory sinus infection, and ordinarily designated by the term "minor" and commonly performed in the practitioner's or specialist's office, are a source of traumatic infection. These include conchotomy, septum operations, polyp extractions, etc., as well as manipulations of even less extent, ordinarily called "treatments." (See section on "Pathogenesis.")

Trauma frequently appears in the clinical records of cases in which it is not the sole etiologic factor, for instance, trauma through the middle ear or through the nasal accessory sinuses, as in ordinary forms of fracture of the skull. An added etiologic factor under such conditions can be the presence of infection in the latter territories; osteomyelitis of the skull under such conditions is, however, practically speaking, unknown. This is undoubtedly so because a flare-up of infection under such conditions commonly results fatally before any bone lesion can develop.

Nevertheless, I believe that primary infection of the skull produced by trauma involving a contiguous area of the skull and of the nasal accessory sinuses undoubtedly occurs oftener than is apparent in the various clinical records. I can remember only one such case in private practice. It must be true that when the patient recovers from the injury only mild forms of bone infection exist, and these are unrecognized in a complex of subjective and objective symptoms which are usually referred to an inflammation of one or more of the nasal accessory sinuses.

A particularly interesting case is the following in which undoubtedly nutritional changes produced by the preceding radiotherapy played an important rôle in addition to the trauma.

In a 48 year old man a blow was sustained to that part of the head where an epithelioma of the scalp had been destroyed by radiotherapy ten years previously.

The scalp broke down and ulcerated, and healing never took place; biopsy showed no malignant condition. On exploration, osteomyelitis was demonstrated in the bone. The bacteriologic content was *Staphylococcus aureus*. The patient died. Postmortem examination showed, in addition, an epidural and subdural extra-cortical abscess, with thrombophlebitis of the cerebral veins and sinuses.

#### HEMATOGENOUS CASES

The mechanism of the pathogenesis and pathology of hematogenous osteomyelitis in general has been discussed extensively on a number of previous occasions,<sup>16</sup> and an extensive discussion of this subject will not be repeated here. Suffice it to say in résumé that acute hematogenous osteomyelitis is a metastatic lesion during the course of a bacteremia, the latter resulting from a bacterial lesion on a surface of the body which forms the portal of entry for the infection. In this conception a surface of the body includes not only the skin, but also the entire mucous membrane of the alimentary tract, the genito-urinary tract, etc. The common surface lesions include not only furuncles, carbuncles, etc., on the skin but also easily demonstrable lesions in the tonsils and in other lymphadenoid collections lying in the mucous membrane of the pharynx, as well as less demonstrable lesions, such as those in the Peyer's patches.

The fundamental cause of the spreading of the original lesion in the form of metastatic or subsidiary lesions is an infected thrombus lying in the original area of infection and communicating at some point with the freely circulating blood. Organisms growing on the surfaces of the thrombus are discharged, or minute pieces of the thrombus laden with bacteria break off and are discharged into the circulation and, becoming lodged for various reasons in the vascular network of various parts of the body, give rise to secondary lesions. Bone tissue, because of its peculiarities in vascular structure, seems particularly prone to the blocking of these thrombi-emboli, and the susceptibility to this is particularly increased during the period of growth when the individual bones contain well marked hyperemic areas at the junction of the diaphysis and epiphysis, around centers of ossification, etc.

The various accessory causes, such as trauma, that determine the localization of a secondary focus of infection—fixation point—in a given bone are associated with accidents in the local circulation which facilitate blocking of any bacterial thrombus-embolus. (See section on "Traumatic Cranial Osteomyelitis.") The essential nature of the patho-

16. Wilensky, A. O.: *Ann. Surg.* **82**:781 (Nov.) 1925; *Am. J. Roentgenol.* **16**:123 (Aug.) 1926; *The Mechanism of Bacterial Infection*, *Arch. Surg.* **13**:228 (Aug.) 1926; *Ann. Surg.* **84**:651 (Nov.) 1926; **85**:428 (March) 1927; *Am. J. Surg.* **3**:281 (Sept.) 1927; *Treatment of Infection*, *Arch. Surg.* **15**:737 (Nov.) 1927.

logic process that develops at the fixation point is a thrombo-arteritis or thrombophlebitis, and the process in the skull is exactly similar to that in other bones in which a dominating position is assumed by the secondary vascular thromboses which must necessarily occur in such a pathologic lesion. The all important secondary effects that these thromboses produce are disturbances of essential nutrition which lead to the death of certain bone cells and the consequent necrosis of certain areas of bone tissue.

The actual pathogenesis and pathology in osteomyelitis of the skull are exactly similar to those in other bones of the body the seat of hematogenous osteomyelitis. The point of fixation in the vascular channels of the skull develops into a thrombophlebitis. The occlusion of the vascular channel or channels results in the usual deprivation of blood supply and nourishment, and the amount, degree and character of the resultant necrosis is in direct proportion to the number, size or importance of the vascular channel occluded and the amount of available collateral circulation.

In hematogenous osteomyelitis of the skull, gross trauma to the skull is frequently an important item in determining the localization of the infection in the cranial bones. The following remarks should be compared with those made in the section on "Traumatic Cranial Osteomyelitis."

2. *Traumatic Hematogenous Cranial Osteomyelitis.*—The reception of an injury to the head, whether or not it results in a closed or open wound, and whether or not the latter reaches down into the bone tissue, may lead to an osteomyelitis of the skull as a result of a hematogenous infection, in which the trauma functions merely by creating a point of least resistance for the blockage of any pathogenic bacteria circulating in the blood as a result of a temporary or established bacteremia. This results in the ordinary form of acute hematogenous osteomyelitis. Most of the cases in the older literature described as due to trauma belong in this group, although lack of accurate knowledge has caused them erroneously to be termed "primary" cases.

Illustrative cases are the following:

A case in which the patient struck the forehead against a bench during an acute catarrhal condition of the nasal cavities (Donalies<sup>17</sup>).

A case in which an injury to the head was sustained while the patient was in a bath tub (Schmiegelow<sup>18</sup>).

In the hematogenous variety of osteomyelitis of the skull certain differences are discernible for which the physical basis is the situation

17. Donalies: Arch. f. Ohren-, Nasen- u. Kehlkopfh. **75**:199, 1908.

18. Schmiegelow, E.: Monatschr. f. Ohrenh., 1905, p. 582.

of the lesion in the network of diploic veins. In the long bones, the situation of the thrombophlebitis in an arterial trunk results in a localization which determines more or less a fixed area of bone which will subsequently necrose and sequestrate. In the diploic veins of the skull, the open wide venous channels encourage, promote and facilitate a progressive continuation of the thrombotic process in all directions. In other words, the process is not stationary; this corresponds clinically to the tendency for the osteomyelitis to spread over wide areas of the cranium.

In actual practice, the classification of a given case, while usually more or less easily done, is on occasion a most difficult one. Given a case, for instance, in which a severe (gangrenous) inflammation is present in the frontal or other nasal accessory sinus and an osteomyelitis is present in the contiguous portion of the skull, it might easily be that either had preceded and caused the other; that is, it could just as readily be hematogenous, as an extension form of osteomyelitis. Usually the specialistic tendencies of the observer—general surgeon or rhinologist—determine the interpretation, owing to the fact that no sufficiently powerful clinical, laboratory or other evidence can be mobilized to decide the question. I have such a case in mind:

The history was that symptoms resembling those of the ordinary type of rhinitis were present for one day, and that simultaneously one eye became swollen. The temperature on admission to the hospital was 104 F. The first operation was done on the day of admission to the hospital; an osteomyelitis was present in the appropriate frontal bone. Bacteriologic examination of the pus showed *Staphylococcus aureus*, and the blood culture was positive for the same organism. The patient recovered after a number of operations.

In 1923, Kallenbach<sup>9</sup> was able to find only twenty-two authentic cases of osteomyelitis of the skull in the literature. In seventeen of these there was apparently a hematogenous origin for the infection.

In a case described by Paschen<sup>19</sup> there was osteomyelitis of the right hip joint, of the right clavicle and afterward of the left parietal bone. The time at which the osteomyelitis of the skull began is not known. In Trendel's<sup>10</sup> case, there was disease of both tibiae, both humeri and the left radius and ulna, followed by osteomyelitis of the right parietal bone. The latter began thirteen days after the onset of the osteomyelitis of the long bones. In Scheinziss's<sup>8</sup> case there was an inflammation of the left tibia, right femur, both humeri and, a month later, of the right parietal bone. Two cases of multiple osteomyelitis are also described by Fröhner<sup>10</sup> from the Tübingen clinic. But the route of the infection is not described. In the first, there was osteomyelitis of the occipital bone, the scapula and tibia; in the second, osteomyelitis of the occipital bone with osteomyelitis of both clavicles and the femur. Among these twenty-two cases, there were no metastases in sixteen and metastases in six, but the route of the infection is not described.

19. Paschen, quoted by Kallenbach (footnote 9).

From other sources one can add the following:

BILLROTH.<sup>20</sup>—One case in the temporal fossa after a resection of the elbow, which became infected.

KÜSTER.<sup>21</sup>—One case of osteomyelitis of the frontal bone after a carbuncle of the neck.

VON BERGMANN.<sup>7</sup>—One case of osteomyelitis of the skull after erysipelas.

LEXER.<sup>22</sup>—One case of osteomyelitis of the skull after a furuncle of the knee.

VON BERGMANN.<sup>7</sup>—Two cases of osteomyelitis of the skull without demonstrable cause.

JAYNES.<sup>23</sup>—One case of osteomyelitis of the skull after measles; one case after typhus.

FISCHER.<sup>4</sup>—One case of osteomyelitis of the skull after a "cold." The notes of this case are interesting:

A "cold" had been present for about three weeks in a 39 year old woman, when she suddenly became ill, with a severe chill, high fever, typhoid-like symptoms and pain in the right temporal and parietal regions. About eight days later a painful swelling developed above the right ear. An incision was followed by a discharge of a large amount of pus. The periosteum of the anterior half of the parietal bone was removed, and there were found numerous suppurative foci of pinpoint size. There was a severe edema of the epicranium of the right half of the skull. The left side of the face and the left half of the body were paralyzed. The patient was delirious. Examination of the eyes and ears failed to reveal a demonstrable pathologic process. A radical operation was carried out, following which the patient died in about seven days. The anatomic diagnosis was as follows: purulent osteitis of the parietal bone and purulent pachymeningitis; purulent leptomeningitis of the right convexity of the cerebrum. A microscopic study of a portion of the bone removed by trephination revealed purulent osteitis and suppurative thrombophlebitis of the veins of the bone. Fischer<sup>4</sup> designated this case as primary or idiopathic acute purulent osteitis because the condition was not preceded by trauma to the bones of the skull, and there was no objective finding pointing to tuberculosis or syphilis. No demonstrable pathologic process could be found in the ear.

The records at Mount Sinai contain the following case in which the hematogenous mechanism is undoubted.

In a middle aged man the classic picture of acute osteomyelitis developed in the opposing ends of the tibia and femur, with involvement of the knee. The end-result was an ankylosed knee and with a small discharging sinus, which persisted. Years later a subperiosteal abscess developed over one parietal bone, and bare bone was palpated in the bottom of the wound. There was no other etiologic factor.

Hematogenous infections of the bones of the skull occur in the following associations:

1. Cases following the ordinary local form of infection, as after a carbuncle.

20. Billroth: *Chir. Klin.*, 1871, p. 76.

21. Küster, E.: *Ein chirurgisches Triennium*, Berlin, 1876, pp. 71 and 78.

22. Lexer, E.: *Centralbl. f. Chir.* (Ref) 22:947, 1895.

23. Jaynes, M.: *De ostéomyélite des os du crâne*, Thèse de Paris, 1887.



2. Cases occurring during or following the infectious diseases, as in the following examples:

Among the cases collected by Kallenbach<sup>9</sup> in which the cause was reported, one each was caused by typhoid, influenza, erysipelas, measles and angina; also one was caused by a "cold." Osteomyelitis of the skull developed four months after the typhoid, two weeks after the influenza and a few days after the beginning of the erysipelas, measles and "cold."

3. Cases due to some temporary bacteremia, the primary cause of which is undiscoverable.

4. Cases of osteomyelitis of the skull occurring in patients who have had osteomyelitis of the long bones for a long period of time. The bacteremia, to the intermediation of which the skull focus is due, is more or less intermittent and chronic, and it is more probable, though not certainly so, that it is derived from one or other of the preexisting bone lesions, rather than from the original primary lesion to which all of the osteomyelitis foci are secondary. At any rate, this has been my experience.

*Relation to Other Foci of Osteomyelitis.*—In most of the reported cases other foci of osteomyelitis coexisted, preexisted or followed the development of osteomyelitis of the skull. I have been able to find one case in the literature in which a second focus developed after the full development of osteomyelitis of the skull. This was in a case reported by Lexer<sup>22</sup> in which on the day after operation for osteomyelitis of the right frontal bone metastasis developed in the right calcaneus.

*Symptomatology.*—The clinical picture in hematogenous infection of the skull is similar in its early stages to that of similar forms of osteomyelitis in general.

In the very severe forms of illness in which hematogenous osteomyelitis of the skull is part of the clinical picture, the severe manifestations—fever, chills and other signs of general infection, including positive blood cultures—are not necessarily to be associated exclusively with the lesions of the cranial bone. All too frequently the skull process is quickly associated with intracranial complications, and it is more to the point to associate the severe clinical manifestations with these rather than with the bone infection. Commonly, it is clinically manifest that the osteomyelitis of the skull is but an incident in a complex, the essential characteristic of which is a general infection of the body.

In the cases of osteomyelitis of the skull of moderate severity, as in all cases of osteomyelitis, there are general symptoms such as fever, chills, etc. Generally speaking, a focus of osteomyelitis is present with well marked local signs and symptoms but without any clinical signs of a general blood infection. A bacteremia is not present. The physical basis for this variety lies (a) in a primary and temporary bacter-

emia, (b) in the development of a fixation point in a bone and (c) in the subsequent spontaneous disappearance of the bacteremia.

In actual practice, the illness commences suddenly, sometimes spontaneously, at other times after an injury often slight in nature. There are malaise, local pain and fever often accompanied by an initial rigor; but when the patient comes under observation he does not present the aspect of extreme illness usually observed in an acute infection of any of the other bones of the body. The grade of these symptoms corresponds to the grade of the local lesion and the extent of the lesion. The outer or inner table only may be affected, or the whole thickness of the bone may be diseased.

In the cases in which the external table only is involved, signs commence to be discernible at the actual seat of the disease almost immediately. The signs consist in the development of an indefinitely demarcated and widespread edematous swelling and tenderness over the appropriate part of the skull. This swelling is rarely detected before the second or third day, and in many of the recorded cases not until later. The swelling may spread in any direction, and a most striking characteristic is the widespread area of the soft parts affected compared with the extent of the bone disease. Presently and quickly these swellings undergo liquefaction, and they are recognizable as subperiosteal (subepicranial) and subcutaneous abscesses of the scalp.

In the cases in which the internal table is involved alone, these local symptoms do not appear; one only has the subjective symptom of pain. Deep-seated fixed pain is, at first, the only sign of mischief; there is no swelling of the soft parts so long as the outer table of the skull remains unaffected, and the patient may perhaps die without there having been the slightest suspicion of the exact state of the bone.

Pain also takes the guise of a diffuse headache with a slightly more definable area over the local disease where the pain is intensified. The pain persists and increases and is controlled with difficulty by the usual means. Headache seems more marked when the internal table is involved to the largest extent or to the exclusion, apparently, of the external table; this is so because of the formation of extradural (subperiosteal) abscesses and their comparative intracranial compressive effects. Practically speaking, this is the entire symptomatology of osteomyelitis of the skull *per se*.

In superficial osteomyelitis of the bones of the skull, the suppuration, of which there is generally speaking no very great quantity, finds a ready outlet through openings in the skin. But where the bone is perforated in its whole depth, retention of pus may occur, and the latter accumulates between the bone and the dura mater; a small portion only makes its way toward the skin, which, if unbroken, will present an indolent, apparently well circumscribed swelling, the main characteristic

of which is that it disappears under slight pressure but soon reappears, more or less quickly according to the position of the patient's head. When this swelling is opened, the pus flows in much larger quantities than would have been expected from the apparent size of the abscess; its escape is not influenced by pressure, but it may be made to stream out by a forced expiration, the mouth and nose being closed.

In the late stages, the clinical picture is distorted, and the symptom complex referable to the bone lesion itself is lost in more dominating evidences of intracranial lesions which secondarily complicate the osteomyelitis. These will be discussed in the section on "Complications."

#### EXTENSION CASES

Most of the cases of cranial osteomyelitis that one sees in hospital and private practice should be classified as extension cases. By that I mean that the osteomyelitis of the cranial bones is due to a spontaneous extension of the inflammatory process in the vascular or lymphatic channels, singly or combined, through contiguity of tissue into the skull bones from a focus of infection in a definite anatomically defined area contiguous to the bone, i. e., from a frontal sinusitis, etc.

The subgroups are as follows: (1) extension from an infection in the soft parts, (2) extension from a focus of osteomyelitis in the superior maxilla, (3) extension from a focus of infection in any or all of the nasal accessory sinuses: frontal, ethmoidal, sphenoidal and antral, and (4) extension from a focus of infection in the otologic apparatus.

*Extension from an Infection in the Soft Parts.*—Extension from an infection in the soft parts to the bones of the skull in the absence of an incomplete or complete fracture seems never to occur or to occur with extreme rarity. Kallenbach's<sup>9</sup> figures are most interesting:

In a period of ten years, ninety injuries of the soft parts of the head were treated, none of which led to osteomyelitis of the skull. Fifty-five injuries of the skull were also treated, among them twenty-two complicated fractures, none of which resulted in osteomyelitis. There was no osteomyelitis of the skull in twelve cases of erysipelas of the head, three cases of phlegmon of the head, two of abscess of the head and two of furuncle of the head.

I have had one experience of this kind.

About ten years ago, I saw a man in consultation in whom a gangrenous infection of the scalp was present. The etiology was obscure. At the time I saw him, the necrotic part of the scalp had separated for the greatest part of the involved area; the cranium lying directly underneath was also necrotic, and numerous small sequestrums could be picked away.

*Extension from a Focus of Osteomyelitis of the Superior Maxilla.*—The physical connection of the superior maxilla with the cranium at

the articulation between its nasal process and the frontal bone makes it possible for an osteomyelitis of the superior maxilla to extend into the cranium. This is possible in the group of cases of osteomyelitis of the superior maxilla which occur in nurslings and infants as well as in a large group in which an infection is present in the antrum and in the bone, and in which it is sometimes difficult to say which of the two is primary. This part of the problem is discussed more fully in the section on antral disease.

*Extension from a Focus of Infection in the Nasal Accessory Sinuses.*—There will be no attempt made to discuss the essential nature of nasal accessory sinus disease as this is not my subject. Only that part of it that seems necessary to the proper explanation of the mechanism by which osteomyelitis of the skull bones complicates accessory sinus disease will be included. In considering this subject, it is to be remembered that not infrequently caries and necrosis of portions of the bony wall of the nasal accessory sinuses occur as part of the pathologic process incident to sinus disease itself; the bone involvement is strictly limited in extent to the area of the latter and directly underlies the affected portion of the mucous membrane. This is the so-called "sinusitis abscondens." It shows little tendency to spread beyond the limits indicated, and surgical intervention of a comparatively simple kind results in a cure. This type and variety of osteomyelitis is also not included in this communication.

Up to the present time, accurate scientific knowledge concerning the pathogenesis and mechanism of osteomyelitis of the skull complicating accessory nasal sinus disease is mostly due to the work of Schilling,<sup>24</sup> Röpke,<sup>25</sup> Gerber<sup>26</sup> and Luc.<sup>5</sup> A résumé of the available literature of importance was made in 1913 by McKenzie,<sup>27</sup> who collated the knowledge of the subject up to that date, the important contributions having been made from German and French sources. The original paper of Schilling<sup>24</sup> contained nine cases; Gerber<sup>26</sup> added twenty, and Luc increased the total number of reported observations to thirty-nine. McKenzie<sup>27</sup> added seven cases. Burger<sup>28</sup> had one case of osteomyelitis of the frontal bone in a total of nine cases of accessory sinus disease with intracranial complications—this in a large private practice of over

24. Schilling, R.: Ztschr. f. Ohrenh. 48:52, 1904.

25. Röpke, F.: J. Laryng., 1899; Verhandl. d. deutsch. otol. Gesellsch., 1907, p. 162.

26. Gerber, P. H.: Die Komplikationen der Stirnhohlentzündungen, Berlin, S. Karger, 1909.

27. McKenzie, D.: J. Laryng. 28:6, 79 and 129, 1913.

28. Burger, in Denkler and Kahler: Handbuch der Nasen-Ohrenheilkunde, Berlin, Julius Springer, 1926, p. 905.

thirty years' extent. In 1926, Bulson<sup>29</sup> was able to find only fifty-five cases in the literature of the preceding thirty years. The figures do not indicate at all accurately the numbers of these cases that have and do continue to occur in practice; but, I believe, they reflect fairly accurately the fact that osteomyelitis of the skull as a complication of nasal accessory sinus disease is relatively uncommon.

Between 1924 and 1931, twelve patients were admitted to Mount Sinai Hospital with some form of osteomyelitis complicated by nasal accessory sinus disease.

The cases at Mount Sinai were distributed according to age as follows:

Up to 10 years	3 cases
11 to 20 years	3 cases
21 to 30 years	1 case
31 to 40 years	1 case
41 to 50 years	2 cases
51 to 60 years	2 cases

Most of Burger's<sup>28</sup> patients were between 11 and 30 years old. In Gerber's<sup>26</sup> twenty-nine cases, the distribution according to age was:

0-10 years	1 case
11-20 years	4 cases
21-30 years	11 cases
31-40 years	3 cases
41-50 years	3 cases
51-60 years	0 cases
Over 60 years	1 case

In the observations up to now, the female sex preponderates. The ratio to the male sex is 8:1 according to Schilling,<sup>24</sup> 11:5 according to Röpke,<sup>25</sup> 16:9 according to Burger<sup>28</sup> and 13:14 according to Gerber.<sup>26</sup> Gerber does not believe that from these figures one may draw a conclusion regarding the preponderance of the female. At any rate, this seems to be of little importance.

*Location of Original Sinusitis.*—As regards the accessory sinus in which the infection originated, it must be remembered that in clinical practice there seems to be no limitation of the infected area to any regional group of sinuses; indeed, the usual thing is to find a diffuse process involving all of the accessory sinus groups. And, if, as sometimes happens, there seems to be a starting point for the infection at some particular point, the spread from the latter to the others is extremely rapid. It would be better to say that the sinus infection, although multiple, seems to exhibit greater manifestations in one or the other groups of nasal accessory sinuses.

29. Bulson, A. E.: Osteomyelitis of the Frontal Bone as a Complication of Frontal Sinusitis, J. A. M. A. 86:246 (Jan. 23) 1926.

With these criteria in mind, it would, then, be proper to accept McKenzie's<sup>27</sup> figures in which he reports the proportions of the cases of osteomyelitis of the cranium as having occurred forty-five times as a consequence of frontal sinus disease as opposed to three times as a consequence of antral disease, these figures being based on the total number of forty-eight cases.

McKenzie<sup>27</sup> was able to find but one case originating in the ethmoid cells—a case of van den Wildenberg.<sup>30</sup> In this case a small sequestrum of the os unguis was first removed, and fourteen days later a large sequestrum comprising the crista galli and the lamina cribrosa. From observations to be detailed subsequently, I am inclined to agree with van den Wildenberg<sup>30</sup> and to disagree with McKenzie,<sup>27</sup> who wishes to classify this also as having originated in the frontal sinus. In this con-

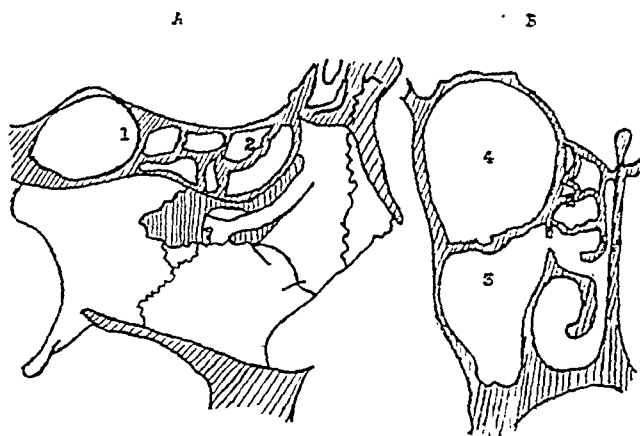


Fig. 4.—Anatomic relationship of the various sinus groups. *A*, anteroposterior section; *B*, transverse section; 1, sphenoid group; 2, ethmoid group; 3, antrum; 4, orbit. (After Katz and Blumenfeld: *Handbuch der speziellen Chirurgie des Ohren und des oberen Luftweges*, Leipzig, 1923.)

nection the case of Sir St. Clair Thomson,<sup>31</sup> to which McKenzie makes reference, had better be omitted from the discussion at present inasmuch as the mechanism was complicated by the performance of an operation.

The experience of other surgeons varies. Thus, Jansen<sup>32</sup> in ten instances, Röpke<sup>25</sup> in thirty-seven, Killian in sixteen and Luc<sup>5</sup> in four found the ethmoidal cells affected along with the frontal sinus. Walker-Downie<sup>33</sup> noted ethmoidal disease in five of six cases. On the other hand, Lermoyez,<sup>34</sup> in thirty-six instances in which the frontal sinus was

30. van den Wildenberg, quoted by McKenzie (footnote 27).

31. Thomson, St. Clair: *Lancet* 2:431, 1905.

32. Jansen, A.: *Arch. f. Laryng. u. Rhin.* 6:355, 1893.

33. Walker-Downie: *Glasgow M. J.*, March, 1899.

34. Lermoyez: *Ann. d. mal. de l'oreille, du larynx* 28:593 (Nov.) 1902.

affected, found only two with associated ethmoidal disease; while Herbert Tilley<sup>36</sup> in twenty-five diseased frontal sinuses noted six with ethmoidal suppuration. Milligan<sup>35</sup> described disease of the ethmoidal cells in eighteen of forty-one cases, while of twenty diseased frontal sinuses, observed by Turner,<sup>30</sup> the ethmoidal cells were also affected in twelve. In Wertheim's<sup>37</sup> postmortem observations, the ethmoidal cells were found affected in seven of twelve cases. In a total of 206 instances in which chronic suppuration of the frontal sinus existed, the ethmoidal cells were implicated in 117, i. e., in 56 per cent.

Among twelve cases of osteomyelitis of the skull after nasal accessory sinus disease in the records at Mount Sinai Hospital, the distribution of the original sinus disease was as follows:

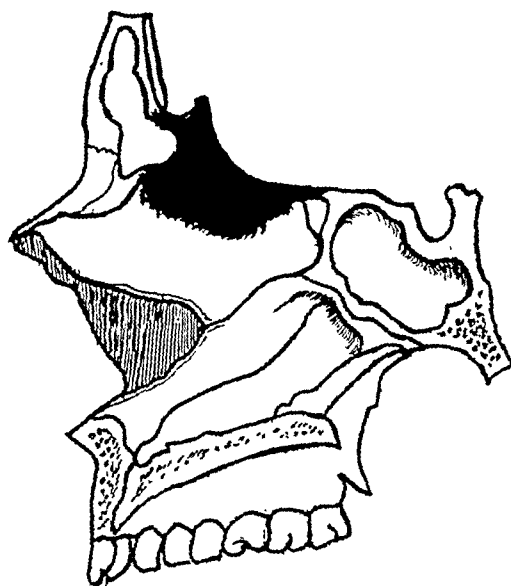


Fig. 5.—Diagrammatic representation of one of the typical sequestrations that occur in the ethmoid group of cases.

Frontal	6 times
Ethmoid	2 times
Sphenoid	2 times
Frontal and ethmoid	1 time
Sphenoid and ethmoid	1 time

I was unable to find any case of osteomyelitis of the skull after disease of the antrum in the records at Mount Sinai Hospital.

It is difficult to assign a cause for the appreciable variance in the individual compilations of cases. One of the things to be remembered

35. Milligan: Brit. M. J., 1905, vol. 1.

36. Turner: Edinburgh M. J. **17**:231, 1905.

37. Wertheim, E.: Arch. f. Laryng. u. Rhin., 1901, vol. 10.

is that the differentiation of the areas that seem to bear the major part of the infection in the general range of the nasal accessory sinus groups is always more or less dependent on the individual interpretation of the objective findings. This could account for the differences in the available statistics.

*Varieties of Sinusitis.*—Osteomyelitis of the skull follows both the acute and the chronic variety of nasal accessory sinusitis. It is altogether likely that even in cases of chronic sinusitis, the occurrence of the bone complication is always in association with an acute flare-up of infection and a spread of the latter into new areas. The only possible exceptions to this statement are found in the simple perforations. See the paragraphs relating to this.

*Bacteriology.*—The bacteriology of osteomyelitis of the skull under the conditions discussed in this communication must necessarily be somewhat uncertain as the bacteriologic findings frequently must show contaminations with other organisms, the habitat of which under normal conditions is the nose and the nasal accessory sinuses. The usual bacteriologic findings described in the literature include *Staphylococcus aureus*, streptococci and pneumococci. The statement is made by Skillern<sup>38</sup> in discussing Woodward's<sup>39</sup> paper that the cases due to *Staphylococcus aureus* all progress well and that those due to the streptococcus and the pneumococcus are all fatal. The observation is apparently not sufficiently supported by bacteriologic evidence and needs considerable confirmation before it ought to be accepted.

In the cases at Mount Sinai Hospital the available bacteriologic data in the cases of cranial osteomyelitis derived from nasal accessory sinus disease are as follows:

<i>Staphylococcus aureus</i>	1 time
<i>Staphylococcus aureus</i> and streptococcus	1 time
<i>Staphylococcus albus</i>	1 time
Streptococcus	1 time
Streptococcus haemolyticus	2 times
Pneumococcus	1 time
Friedländer bacillus	1 time

*Varieties of Osteomyelitic Bone Lesions Found.*—In the literature the varieties of osteomyelitis of the skull that complicate nasal accessory sinus disease have been differentiated and classified on the basis of the extent of the lesion and the rapidity of spread of the pathologic process. This form of classification seems to be a good one and will be followed in this communication also. Clinically, the following are found:

38. Skillern, R. H., in discussion on Woodward (footnote 39).

39. Woodward, F. D.: Osteomyelitis of the Skull, J. A. M. A. 95:927 (Sept. 27) 1930.



1. *Perforating Lesions*: In a certain number of the cases this form is associated with insufficient or absent drainage from the normal ducts, and the character of the pathologic process leads one to believe that the process is just what its name implies—a simple perforation. It is questionable whether this form ought to be classified as osteomyelitis; personally, I do not think so.

Perforation is quite common, however, with well marked and more widely spread evidence of true inflammation of bone and of necrosis and sequestrum formation. In these, the diagnosis of osteomyelitis is never in doubt; and the matter of the perforation—in contradistinction to the type just described, in which it is just an attempt on nature's part to secure drainage—is a matter of little importance in the total clinical and pathologic picture.

Perforations are found to complicate both the acute and the chronic type of accessory sinus disease.

2. *Localized Lesions*: In this variety the tendency is exhibited for the lesion to remain relatively localized and the development of the process is relatively slow, taking months and sometimes years. Exacerbations of infection are, however, very common, and in such an exacerbation the tendency of remaining localized may be lost; then the process spreads with great rapidity over a large part of, or the entire, skull, as is characteristic of the unrestricted variety to be immediately described.

3. *Spreading and Diffuse Lesions*: There is a certain amount of overlapping between the cases in this group and those in the preceding group, and the physical characteristics of the pathologic process in the cases in this group frequently and commonly also include those of cases in the preceding groups. Clinically, the manifestations may or may not begin with the milder symptoms of the cases in groups 1 and 2; but the great differentiating factor consists in the fact that the relatively benign characteristics of a localized lesion are lost, and the spread of the osteomyelitis becomes unrestricted and extends to the major portion or to the entire extent of the cranium. One must distinguish the diffuse form from the circumscribed form of osteomyelitis, which has a tendency to heal. The diffuse form has a tendency to spread over the entire skull and presents an almost absolutely unfavorable prognosis.

Relative lack of constitutional resistance and relative extreme virulence of the infecting organism have furnished the explanation why one patient does, and the others do not, develop osteomyelitis under apparently precisely similar conditions. The process may seemingly be a unilateral one and limit itself to the bones of one half of the cranium, or, more commonly, it spreads on both sides of the skull. The development of the diffuse form of the osteomyelitis or its extension from more localized forms may occur rapidly, especially in young patients, or, on the contrary, months may be required for the process to evolve.

In Tilley's<sup>6</sup> case, a most extreme one, the process spread upward over the entire vault of the cranium and then downward on each side to and including the petrous pyramid.

*Pathogenesis in Cases Following Nasal Accessory Sinus Disease.*—The nature of the illness and of its origin in an infection of the nasal accessory sinuses is such as to prevent one from securing specimens of the lesion that would demonstrate the early stages when the transmission of the pathologic process occurs into the bone tissue. Beliefs recorded in the literature regarding the paths and the methods of propagation into the bone tissue are therefore necessarily assumptions based on clinical observations and pathologico-anatomic evidence obtained from specimens in a late stage of the lesion.

In the literature, three methods of infection have been suggested:

1. The infection is described as a direct invasion by the organisms of infection of the canalicular and medullary spaces of the bone tissue from the inflamed area of the lining mucous membrane of the given nasal accessory sinus. Preference is given entirely to this method by McKenzie,<sup>27</sup> and, only under certain conditions, by Schilling (i. e., when the diploic tissue abuts on the wall of the frontal sinus, as, for example, in the neighborhood of the upper recess).

McKenzie<sup>27</sup> is inclined to minimize the part played by the diploe of the bone in relation to the sinus, so emphasized by the continental authors, who contend that the proximity of the diploe to the diseased cavity, or its surgical exposure, lays it open to infection. While he believes that the infection may be able to spread more rapidly once the diploe has been reached, he holds that diffuse osteomyelitis is not limited in its spread to diploic bone only.

2. Another group of observers describe the infection as spreading to the bone tissue by the small veins of the mucous membrane of the accessory sinuses, which in turn communicates with the diploic veins. In Laurens'<sup>40</sup> case, it was possible to demonstrate the thrombosis of the diploic veins far in advance of the maturely developed lesion in the skull. It is generally believed that the unrestricted extension of the osteomyelitis in the cranium is due to this variety of mechanism.

3. McKenzie<sup>27</sup> speaks of a "general advance" of the pathologic process which, to him, does not seem to select any particular path. As evidence for this conception, he cites Wylie's case in which bacteria were demonstrated in the haversian canals and under the periosteum, as well as in the diploic spaces and tissues. This suggestion is not difficult to understand. It probably refers to comparatively late cases in which the pathologic process is so widespread in the microscopic picture as to give

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40. Laurens, quoted by McKenzie (footnote 27).

the impression that all available paths are being utilized in the spread of the process. This, of course, does not give the true picture.

All three of these methods of spread of the infection are necessarily correct in the observation that the essential part of the process is the spread into the diploic veins. In the light of modern conceptions of disease and of bacteriologic and pathologico-anatomic knowledge, I believe that the following statements may be taken as correct:

There is absolutely no clinical or laboratory evidence to show that the occurrence of the osteomyelitis as a complication of nasal accessory sinus disease is ever due to a hematogenous infection, i. e., that a bacteremia first occurs with the primary lesion in the mucous membrane of any of the nasal accessory sinuses, and that the osteomyelitis is a secondary (metastatic) lesion therefrom. The clinical evidence bears abundant proof, and this is borne out by anatomic and histologic studies (Schilling,<sup>24</sup> Laurens,<sup>40</sup> Wylie<sup>41</sup> and others) that the osteomyelitis of the frontal bone or of the skull is due to (a) either a spontaneous extension of the pathologic process along contiguous structures and paths, (b) or a direct primary infection of bone tissue during the course of some operative trauma; that is, cases of osteomyelitis of the skull complicating nasal accessory sinus disease are either extension cases or primary cases of osteomyelitis. (See the section on "Traumatic Cranial Osteomyelitis.")

(a) Spontaneous Cases: In the cases in which the osteomyelitis is a spontaneous complication, the mechanism of the extension of the process into the cranial bone must necessarily depend on two factors: (a) On the bacteria involved in the infection with especial reference to the relative preponderance of virulence of the organism and of the opposing strength of natural resistance. This is important because, otherwise, it might be difficult to explain the occurrence of the osteomyelitis in one patient and its nonoccurrence in others, in all of whom all of the other factors are seemingly identical. (b) On the character of the anatomic structures involved with special reference to the structure of the osseous tissue and the arrangement of the arterial and venous network.

According to Gray in his "Anatomy of the Human Body":

The flat bones of the skull are composed of two layers of compact tissue enclosing between them a variable amount of cancellous tissue. These layers are the outer and inner tables of the skull. The outer one is thick and tough; the inner one is thinner, but of denser structure, and more brittle (i. e., the vitreous table). The intervening cancellous tissue is the diploe.

The walls of the frontal sinuses are composed of thin plates of compact bone which make up the anterior, posterior and superior walls of the sinus. Only where the superior and anterior walls meet to form the superior recess does the compact tissue divide into two tables to include a diploe. Just how far the diploe

41. Wylie, A.: *Lancet* 1:178 (Feb. 1) 1919.

extends into the superior and anterior walls is an individual matter; but only in exceptional cases does the diploe extend into these walls for any appreciable distance.

The structure of the irregular bones at the base of the skull is of two varieties. At certain areas, notably where the body of the sphenoid articulates with the occipital, the structure resembles that of other irregular bones, such as the vertebrae: a peripheral layer of compact tissue surrounds a core of cancellous bone. Elsewhere in these bones, the structural masses consist of a series of cellular chambers formed by thin bony plates in which cancellous tissue is for practical purposes absent. At any rate, except at the points indicated there is no direct connection between the cancellous tissue of these bones and the cranial diploe.

These anatomic facts provide the physical basis for the variety of clinical lesions which occur spontaneously as follows:

In simple perforation the chances of the infectious process, under pressure of retained pus and insufficient drainage from the sinus, perforating at any other part than through the thin, bony, plate-like walls is relatively rare. The chances of the perforation in the thin, bony plate lying in an area bearing diploic structure depends on the individual distribution of diploe and is relatively very little. This is borne out by clinical observations and anatomic studies. Simple perforation is always seen through the thin, bony, plate-like walls; perforation elsewhere is usually an incident in a much more widely spread area of osteomyelitis; penetration into the diploe is a much more unusual phenomenon and is always the forerunner of extensive areas of osteomyelitis, and the relatively greater numbers of this complication occurring with frontal sinus disease than with disease in any of the other accessory sinuses are due to the relative and actual sparsity of physical connection between any diploic tissue in the bony walls of the latter accessory sinuses as opposed to the direct connection of the frontal diploe with that of the rest of the cranium. Osteomyelitis is produced in this way by the mechanical introduction of the infection into the diploe.

Other forms, or more extensive forms of osteomyelitis occurring spontaneously with accessory sinus disease, are due to extension of a phlebotic lesion along the vascular channels into the diploe.

According to Gray:

The diploe of the cranial bones is channeled in the adult by a number of tortuous canals, which are lined by a more or less complete layer of compact tissue and contain a network of veins.

The latter are large and capacious, their walls being thin, and formed only of endothelium resting upon a layer of elastic tissue, and they present at irregular intervals pouch-like dilatations, or culs-de-sacs, which serve as reservoirs for the blood. These are the veins of the diploe; they can only be displayed by removing the outer table of the skull.

As long as the cranial bones are distinct and separable, these veins are confined to the particular bones; but when the sutures are united they communicate with each other and increase in size.

As regards the spread of infection by the venous channels, in many instances numerous communicating veins are to be seen with the venous channels in the diploe. Once infection has traveled along these channels into the diploe, the conditions are very favorable for an extension of the inflammatory process further along between the tables of the skull. This favorable condition in the diploe for the extension of the infection has been definitely proved pathologico-anatomically by several observers (Schilling,<sup>21</sup> Laurens<sup>40</sup> and others). The older the patient, the less barrier there is to the extension of the infection, and, as McKenzie<sup>27</sup> and others have pointed out, in adult life there is a direct continuity of osseous structure between the contiguous bones of the skull and of the diploic veins which traverse the sutures of the skull. Diffuse and rapidly spreading forms of osteomyelitis must necessarily always occur by way of the vascular channels, as once the infection has penetrated into the vascular network no efficient obstacle is present to the further spread of the infection along the veins past the sutures and from one cranial segment to the others.

(b) Postoperative Cases:<sup>42</sup> It would be well to understand at the outset that although the literature speaks at length of cases in which this complication occurs spontaneously, this probably occurs in a much smaller percentage than is apparent. For, the term "operation" should include not only those large manipulations ordinarily dignified by the attachment of some surgeon's name, but also all of those minor manipulations (extraction of polyps, etc.) which are not classified as such, but are called "treatments" of one kind or another and are commonly performed in the practitioner's or specialist's office. These, under proper circumstances which are all too commonly present, can be productive of all grades of traumatism to the soft parts and to the vascular channels.

In spite of the fact that in the literature the total percentage of cases in which osteomyelitis of the skull occurs as a complication of nasal accessory sinus disease is approximately 3, the opinion has become prevalent among otolaryngologists that while osteomyelitis of the skull bones is one of the uncommon spontaneous complications of nasal accessory sinus disease, it is one of the commonest serious sequela of operation for the cure of the latter. This statement seems to hold true for the most part for cases of frontal sinus disease. It holds true to a much less extent for cases of ethmoid sinus disease, and possibly not at all for cases of sphenoid or antral sinus disease. The facts in the matter seem to be as follows:

Gerber's<sup>20</sup> communication lists twenty-nine cases of osteomyelitis of the frontal bone or skull complicating accessory sinus disease. In thirteen of these cases no definite etiology is mentioned; in the other sixteen.

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42. See section on "Traumatic Cranial Osteomyelitis."

influenza, syphilis, trauma, coryza and measles are mentioned as etiologic factors. I, personally, believe that such etiology did not play a rôle in the production of the osteomyelitis, but rather in the production of the original accessory sinus disease. The important point is that among the sixteen cases cited by Gerber,<sup>43</sup> osteomyelitis of the skull followed some operation on the accessory sinuses ten times—a very large proportion.

McKenzie's<sup>47</sup> statistics cover forty-one cases of osteomyelitis of the frontal bone in which the complication developed spontaneously in twenty-one cases and after some form of operation in twenty cases.

In the Mount Sinai group practically all of the cases of osteomyelitis of the skull complicating nasal accessory sinus disease developed prior to the performance of any operation of the Ogston-Luc<sup>43</sup> or Killian<sup>44</sup> types in the hospital. There is a possibility that in some of them at least, some minor forms of "office" operations had been done previously to the admission of the patient to the hospital. In general, the osteomyelitic process was discovered at the time the first operation was done in the hospital. This experience corresponds with that of Burger.

This discrepancy seems to offer insuperable obstacles to adjudication except on the basis of individual interpretations of operative findings. My personal impressions incline me to agree with those who believe that operation is a frequent precursor of the osteomyelitic complication. An examination of all of the factors entering into the various types of operation for nasal accessory sinus disease seems, therefore, in place.

There are two types of operation:

(a) Operations of the Ogston-Luc type consist in opening the frontal sinus through its anterior wall, in careful curetting of its interior, in establishing a large communication between the sinus and the nose and at the same time destroying the anterior ethmoid cells in the region of the nasofrontal duct. Drainage into the nose is ensured through the nasofrontal aperture, and the operation is completed by immediate suture of the skin incision.

Probably no other type of operation has been more generally performed on the frontal sinus, yet because of anatomic structure, clinical evidence has been very much against the performance of an operation that does not permit of thorough inspection of the entire sinus and of the ethmoid cells. In order to bring this about, it is necessary to remove the whole of the anterior wall of the sinus, and also to a greater or lesser extent the floor. By such a procedure one is able to inspect the whole interior of the cavity thoroughly, however large it may be; no

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43. Ogston-Luc: *München. med. Wchnschr.*, 1895, no. 28.

44. Killian: *Ztschr. f. Ohrenh.* 37:343, 1900; *Arch. f. Laryng. u. Rhin.* 1902, vol. 13.

recess can escape one's observation; the septum between the two cavities can be examined, and the presence of ethmoid cell extension into the orbital roof will thus not be overlooked.

(b) This is the reason and the basis for the modern Killian type of operation. The whole sinus, with its recesses and partitions, is thoroughly inspected, and the cavity is almost completely obliterated by the resection of its anterior and inferior bony walls. Further, by the removal of the ascending or frontal process of the superior maxilla, excellent access is obtained to the ethmoid cells, and a large opening of communication is thus made between the frontal sinus and the nasal cavity, so that good drainage into the nose can be established.

Two factors are constantly present in all cases in which operation is done for nasal accessory sinus disease:

(a) Infection is always present, and the operation must necessarily be done through infected territory. The only possibility of preventing this would be to so arrange the steps of the operation as to remove the entire infected area in one segment, a procedure which, while possibly technically feasible, would be unwarranted for any and all other reasons, would result in a deformity of contour that would not be acceptable to either the surgeon or the patient, and would probably yield an enormous mortality. One must content oneself, therefore, with less radical measures—a state of affairs that makes it technically impossible to remove every bit of infected tissue. Foci of infection are, therefore, necessarily left which readily contaminate the newly exposed bone tissue in the operative field.

In those unfortunate cases in which operation is undertaken for the cure of sinus disease, the inflammatory condition is markedly enhanced during the operation. The granulation tissue in the sinus, which has hitherto formed a barrier to the invasion of the organisms, is broken down, and a path is opened, which readily admits of their further spread into the frontal bone.

(b) The second constant factor is operative trauma. The same anatomic studies to which I alluded previously show also why operation for sinus disease is so apt to be complicated by osteomyelitis of the skull. If the operator is not careful, or the anatomic distribution of the diploe is extraordinarily well developed and reaches beyond the usual limits, opening into the diploe by chisel or curet is to be expected and does commonly occur. Infection is then implanted directly into the diploic contents.

An analysis of the cases made by Turner<sup>36</sup> showed that in 74 per cent of the cases in which the osteomyelitis appeared the complication occurred after the sinus was opened and drained (Ogston-Luc type of operation). In 88 per cent of these, death followed a single operation,

while in the remainder more than one operation had been performed, owing to the failure of the first to effect a cure of the suppurative condition. The remaining 24 per cent of the cases all proved fatal after an operation for obliteration of the sinus; in 50 per cent of these, simple opening and draining had been previously performed without success, the more radical method having been a secondary procedure. It is evident, therefore, that a considerably larger proportion of the cases occurred after the Ogston-Luc type of operation than after the operation for obliteration. This general impression is confirmed by Burger.<sup>29</sup>

Consideration of the steps in either form of operation gives an adequate explanation of the results. In the simple (Ogston-Luc) operation, an opening is made into the frontal sinus through its anterior wall. The density of the bone forming the anterior wall of the frontal sinus varies considerably, and anatomic studies have shown that this general area is the one in which the diploic structure is commonly found; whenever, as in some instances, the diploic structure is exaggerated, it spreads downward for a considerable distance. The more the diploe of the walls of the frontal sinus is developed, the greater is the anatomic predisposition for the development of osteomyelitis of the frontal sinus. For this reason, young persons are more predisposed than those of mature age. In the former, the diploe has larger meshes and has a larger supply of vessels than in the latter. Cases in which prior to and during the first operation on the frontal sinus nothing pointed to a disease of the bone, and in which such a disease occurred only after the operation, naturally intensify the feeling that the operation itself was the cause of the infection of the diploe.

The mere chiseling of the anterior wall of the frontal sinus is sufficient to open and to infect the diploe of the frontal bone. This was probably so in the case of St. Clair Thomson and in that of Luc and Lermoyez.

In the radical (Killian type<sup>44</sup>) operation, the complication is not so likely to occur, because one of the points of this type of operation is the retention of as much of the anterior wall of the sinus as is possible, the approach being made through the floor in order to prevent the deformity that accompanies excessive removal of the anterior wall. The floor of the sinus practically never contains diploe, the compact bone tissue of the bony plate does not take up the infection so readily, and the complication therefore appears less often after this type of operation. As a matter of fact, in many of the cases in which this radical type of operation has been done, and in which the osteomyelitis developed, it has been preceded by the simple drainage (Ogston-Luc) type of operation.

Once infection is introduced into the diploe, the physical basis for the localization, the firm lodgement and the spreading of the infectious process depend on the character of the vascular network of the skull and



on whether the infection is lodged (*a'*) in the venous plexus or (*b'*) in an arterial trunk.

(*a'*) In the former, a thrombophlebitis becomes established in the venous plexus of the diploe. The character of the osteomyelitis, whether localized or diffuse, the relative rapidity of spread and any other physical characteristics depend on the area of venous plexus involved in the thrombophlebitis, and on the biologic virulence of the infecting organism as opposed to the natural protective powers of the host.

(*b'*) In the second group, an injury most probably takes place during the course of the operation to an arterial trunk, and a secondary thrombosis occurs in the latter.

According to Gray:

The supra-orbital artery arises from the ophthalmic as that vessel is crossing over the optic nerve. Ascending so as to arise above all the muscles of the orbit, it passes forward, with the supra-orbital nerve, between the periosteum and levator palpebrae; and, passing through the supra-orbital foramen, divides into a superficial and deep branch, which supply the integument, the muscles and the pericranium of the forehead, anastomosing with the frontal the anterior branch of the temporal, and the artery of the opposite side. This artery in the orbit supplies the superior rectus and the levator palpebrae and sends a branch inward, across the pulley of the superior oblique muscle, to supply the parts at the inner canthus. At the supra-orbital foramen it frequently transmits a branch to the diploe.

The ethmoidal branches are two in number—posterior and anterior. The former, which is the smaller, passes through the posterior ethmoidal foramen, supplies the posterior ethmoidal cells, and, entering the cranium, gives off a meningeal branch, which supplies the adjacent dura mater, and nasal branches which descend into the nose through apertures in the cribriform plate, anastomosing with branches of the sphenopalatine. The anterior ethmoidal artery accompanies the nasal nerve through the anterior ethmoidal foramen, supplies the anterior ethmoidal cells and frontal sinuses, and, entering the cranium, gives off a meningeal branch, which supplies the adjacent dura mater and nasal branches, which descend into the nose, through the slit by the side of the crista galli, and, running along the groove on the under surface of the nasal bone, supply the skin of the nose.

The frontal artery, one of the terminal branches of the ophthalmic, passes from the orbit at its inner angle, and, ascending on the forehead, supplies the integument, muscles and pericranium, anastomosing with the supra-orbital artery and with the artery of the opposite side.

The nasal artery, the other terminal branch of the ophthalmic, emerges from the orbit above the tendo oculi, and, after giving a branch to the upper part of the lachrymal sac, divides into two branches, one of which crosses the root of the nose, the transverse nasal, and anastomoses with the angular artery; the other the dorsalis nasi, runs along the dorsum of the nose, supplies its outer surface, and anastomoses with the artery of the opposite side and with the lateral nasal branch of the facial.

Injuries to any of these major arterial channels are accountable for those larger, more or less anatomically well defined areas of osteomyelitis

which result in correspondingly similar masses of sequestered bone. One of these typical clinical entities occurs in the frontal bone. The physical basis for this is undoubtedly injury to the terminal branch of the frontal artery after its emergence through the supra-orbital foramen, which branch supplies, among other structures, the pericardium of the vertical portion of the frontal bone just above the glabella. An arterial lesion of this kind undoubtedly also supplies the physical basis for the lesion described by Smith in which a segment of bone and its corresponding integument exfoliated in one piece. Another example of this type of lesion is the sequestration which occurs in the ethmoid, and for which the physical basis is injury to the ethmoidal arteries. (See under discussion on the frontal and ethmoid groups.)

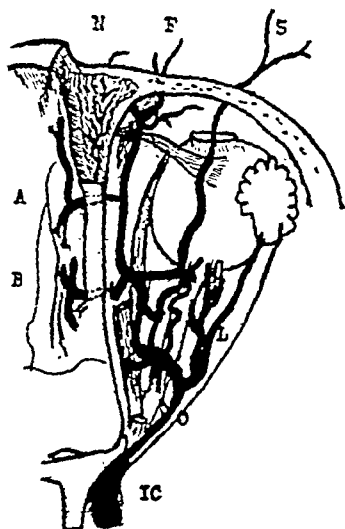


Fig. 6.—Arterial blood supply of the general frontal and ethmoid sinus regions, including that of the orbit. *A*, anterior, and *B*, posterior ethmoidal arteries; *N*, nasal artery; *F*, frontal arteries; *S*, supra-orbital artery; *IC*, internal carotid artery; *O*, ophthalmic artery; *L*, lacrimal artery. (Tracing from Gray's "Anatomy of the Human Body.")

Operative injury, by itself, whether to the venous plexus of the diploe or to a major arterial trunk, would possibly not be sufficient to give rise to osteomyelitis of the skull. The constant presence of virulent organisms, both normally residing in the nasal and nasal accessory cavities, and also present as the inciting agent of the original sinusitis, provides the necessary and essential element for the establishment of an inflammatory lesion in the bone tissue. The operative injury provides a soil of decreased resistance for the growth and development of the organisms, and in the cases of injury to the arterial trunk establishes areas of bone in and from which nourishment by blood supply has been

eliminated. Operative injury plus infection provides the two factors necessary to give the total clinical picture.

The question of drainage after operation is also important. In neither of Lack's fatal cases was the mucous membrane of the sinus curetted, yet an osteomyelitis of the frontal bone supervened, and death followed from intracranial complications. Tilley<sup>6</sup> blames defective drainage into the nose, coupled with complete closure of the skin incision, as a cause of disaster in these cases. Most surgeons will probably agree with the necessity of establishing free drainage, a point that has from time to time been insisted on by the majority of writers on the subject. In two fatal cases, mentioned by Turner,<sup>31</sup> no sutures were placed in the skin incision, thus ensuring free superficial drainage; in one of these, however, the fatal result is attributed to defective nasal drainage; in the other, numerous ethmoidal cells extending into the orbital roof were overlooked, and bone sepsis was thus set up.

I think that Turner's experience is almost sufficient to show that the question of the drainage itself is not of much importance as regards the appearance of the osteomyelitis. The latter, under such circumstances, probably should be explained on the basis discussed in the section devoted to the spontaneous occurrence of this complication after nasal accessory sinus disease.

*Symptomatology in Cases Following Nasal Accessory Sinus Disease.*

—As a general rule, the symptomatology of osteomyelitis of the skull conforms itself to anatomic considerations incident to each sinus group. This is especially so for perforative and localized lesions, and for these reasons the discussion of the symptomatology of these varieties of lesions will be found in the subsequent appropriate sections giving the individual characteristics of each sinus group.

Localized pain and diffuse headache associated in many cases with vomiting are important clinical symptoms. More detailed discussion is found in the individual discussions, especially that related to sphenoid sinus disease.

In severe, spreading and diffuse forms of osteomyelitis of the skull complicating nasal accessory sinus disease, a general similarity of the clinical picture is exhibited by all groups.

Hyperacute cases of osteomyelitis of the skull complicating nasal accessory sinus disease are relatively rare. The clinical picture of the cases in this group is that of a profound general infection: There are marked toxemia and a very severe organic resection. The disease begins with violent chills, and high fever follows; the general condition frequently and suddenly becomes grave, the pulse becomes weak and feeble, the urine is scanty and sometimes contains albumin, diarrhea often

appears, and the patient is prostrated and covered with perspiration. In the most severe cases, death follows in a few hours from the general infection.

In extremely sick patients, alarming secondary intracranial complications develop and the symptomatology of the osteomyelitis is overshadowed by the latter. These will be discussed subsequently and more extensively on another occasion.

A general blood infection (sepsis, septicemia, pyemia) is not commonly demonstrable in uncomplicated cranial osteomyelitis by positive blood cultures. Nevertheless, transient or more prolonged states of blood infection undoubtedly do occur, as in some of the fatal cases lesions are described and are present in organs distant from the seat of the local lesion or its neighborhood, the mechanism for the production of which is surely blood-borne.

Positive blood cultures are uncommon. A positive culture occurred in one of the twelve cases at Mount Sinai Hospital; *Staphylococcus aureus* was recovered. In another case due to infection by the pneumococcus type I, it was suspected that a bacteremia was present; as the patient died two hours after admission, there was no opportunity to prove this. It is my impression that positive blood cultures occur only when meningitis and other similarly grave intracranial complications occur.

*Clinical Course in Cases Following Nasal Accessory Sinus Disease.*—The course of the disease is generally very protracted and is frequently interrupted by intervals of relative euphoria. In Luc's case there was a period of three months between the last manifestation of osteomyelitis and the first one of pachymeningitis; the entire disease lasted two years; a cure was then obtained, which Luc ascribes to the slight virulence of the streptococci. In general, the development of the entire disease and its clinical picture may take as little as two or three months, or as long as two or more years. In the fatal cases the cause of death is much more commonly the effects of the intracranial complications; much less commonly it is the effect of a general blood infection.

A. Special Characteristics in Cases Associated with Frontal Sinus Disease: Cases of frontal sinus disease have formed the bulk of the cases in which osteomyelitis of the skull has complicated the clinical picture; that they have been the basis for most of the reports to be found in the literature.

In Gerber's <sup>26</sup> series of twenty-nine cases the lesion was present as follows:

In the anterior wall	13 times
In the posterior wall	7 times
In the floor	2 times
In all walls	1 time

In frontal sinus disease, perforations occur as follows: (a) In the anterior wall of the frontal sinus. An abscess then forms over the frontal eminence. The spread of this form of abscess is always upward under the scalp.

(b) In the floor of the frontal sinus. A subperiosteal abscess forms that can be palpated as a lump attached to the roof of the orbit. Involvement of the general orbital cavity cannot and does not occur until the orbital periosteum breaks and permits the diffusion of the pus into the orbital cavity. In the late stages, proptosis occurs. This form of abscess never spreads upward under the scalp of the forehead.

(c) In the roof of the frontal sinus. An extradural abscess forms. The further spread of the suppuration occurs by tracking between the dura and the bone, and by increasing accumulations of pus when signs of intracranial compression occur or by perforation through the dura when subdural intracranial complications, to be discussed subsequently, occur.

Localized forms of osteomyelitis complicating frontal sinus disease are found as follows:

(a) Relatively small areas in the anterior wall of the frontal sinus. These are relatively easily recognized by the swelling over the frontal eminences. The lesion tends somewhat to remain localized and, unless spreading of the lesion occurs, give little cause for concern.

(b) Relatively small areas in the superior-posterior recess of the frontal sinus. These are more difficult to recognize, and most commonly presage a later and more widely spread lesion. Intracranial complications occur but not as commonly as in the next variety.

(c) Relatively small areas in the upper angle of the frontal sinus. These, as well as those in group *b*, are difficult to recognize clinically, are apt to grow in size and spread rapidly and unlimitedly, are commonly complicated by intracranial lesions (because the diagnosis is made late), and, because of these facts, have a high mortality.

(d) A characteristic sequestrum. The sequestrum has the shape of a tennis racket, the narrow part occupying the general region of the internal angular process of the frontal part, the flare spreading obliquely upward and outward in the vertical portion of the frontal bone and lying altogether to one side of the median line.

Most of the diffuse forms of osteomyelitis of the skull occur after frontal sinus disease. The direction of spread of the process in the cranial bones is somewhat characteristic: The general tendency is for the process to spread upward and outward from the region of the appropriate sinus into the vertical portion of the frontal bone; then to the parietal and temporal regions, and finally to the occipital bone. There

is no strict limitation of the process to one side of the skull, and although this is the general rule, involvement of the opposite side by contiguity is common. There seems to be little or no tendency for the osteomyelitis to spread into the base of skull when the other sinus groups are uninvolved.

1. Symptomatology and Clinical Course in Cases of Simple Perforation: In cases of simple perforation through the floor of the sinus, the symptomatology is simple, and a diagnosis is easily made. In a patient with symptoms of frontal sinus disease, the orbital fissure narrows, the orbital content becomes swollen and there is a good deal of tearing. Pain is present, or becomes exaggerated. There is usually no fever.

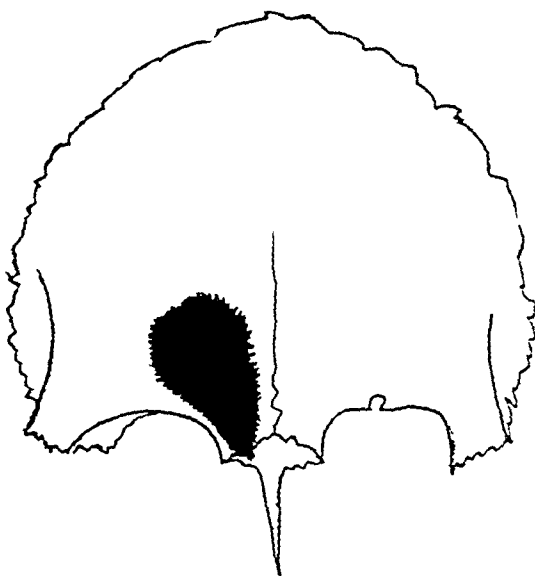


Fig. 7.—Diagrammatic representation of a typical sequestration seen with frontal sinus disease.

Frequently a small mass is felt attached to the roof of the orbit, which is a subperiosteal abscess. If the latter is not promptly incised, and if it should rupture into the orbit, a diffuse orbital phlegmon develops.

In cases of simple perforation through the anterior wall, the symptomatology is also not difficult; the region of the glabella becomes swollen and edematous, and an abscess forms under the skin, which either ruptures spontaneously or is incised. In either case, a probe quickly demonstrates an opening leading into the frontal sinus.

I have come across no case in the literature, nor have I personally seen any case in which simple perforation occurred anywhere else than as indicated in the text.

2. Symptomatology and Clinical Course in the Localized Form: In the ordinary case of an insidious development of an osteomyelitis of

the skull complicating a frontal sinus, the suspicion that the latter is developing does not arise for an appreciable interval. In cases in which operation has not been performed clinically the most important symptom is the extension beyond the borders of the frontal sinus of an edematous swelling combined with an actual doughy infiltration, which extends below the scalp and remains constant when there is free drainage of the pus. Multiple subperiosteal abscesses speak for osteomyelitis, especially if there are concurrent general symptoms. This applies more so when the probe below the galea encounters everywhere rough bone. Morel and Hubert<sup>45</sup> compare the osteomyelitic bone with "rotting wood."

If an operation of the frontal sinus has already preceded, then the beginning of the osteomyelitic complication shows itself first in a reddening, swelling and loosening of the scar. The lifting up of it reveals pus. The probe reveals the conditions just described. These symptoms indicate the necessity for a new operation.

At the secondary operations the wound is enlarged by means of new incisions. The skin is found to be swollen and infiltrated and contains islands of suppuration. The friable and necrotic bone is removed. The subadjacent dura mater is fungous and purulent. The limits of the osteitis are not grossly distinguishable and are reached with difficulty. The bone is always thickened, soft and red. If all of the affected portions are removed, the temperature descends and all the symptoms disappear. But more frequently there is only a period of calm, and on the second or third day the wound suppurates. Cicatrization does not take place; the gangrene extends, and the temperature becomes irregular. A new operation again is indicated, and is then usually done in an attempt to get beyond the diseased area.

This same clinical picture may be reproduced three or four times at more or less long intervals, and a cure may finally be obtained, but in most cases the pain is continuous and the swelling of the wound persists.

In the severe rapidly progressing cases, this always occurs with increasing frequency. New subperiosteal abscesses form. Frequently, in the severe cases, the local symptoms decrease, but the general symptoms increase and the entire organism is invaded by a general blood infection. There is severe intoxication of the organism with chills, profuse perspiration, delirium and remittent fever. There is an increase in the size of the liver and spleen. Death occurs from extension of the infection to the brain, sinuses or lungs, regardless of new operations.

3. Symptomatology and Clinical Course in the Diffuse Form: In the diffuse form, there are certain symptoms that are more or less characteristic. The pain is diffuse, and the patient cannot localize it.

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45. Morel, L. E., and Hubert, C., quoted by Guisez: *Bull. et mém. Soc. franc. d'otol.* 1:1, 1906.

The headache generally is more severe at night, as is the case with all pains of osseous origin. The patient is unable to sleep, and even large doses of opium or narcotics do not relieve the pain. It is generally more marked at the beginning of the condition, but it is very variable. In some cases it does not appear until the end, and it may even be absent.

The swelling around and about the wound is not sharply defined. It may be of a doughy nature, and then it may make one think of an erysipelatous infection. As the process spreads, discrete swellings appear at some little distance; these are subperiosteal abscesses. The skin is red and very tender.

Fever is for the most part continuous, although the curve may fall to normal limits for short intervals only to return promptly. At the onset the temperature is apt to be very high and of an irregular course. During the course of the disease, when the manifestations are particularly severe, the temperature frequently assumes the characteristics customarily seen in typhoid fever. Chills are not common; they occur only in cases of general infection, frequently indicate the presence of a complicating phlebitis of one of the intracranial sinuses, are present with and without positive blood cultures and are generally of unfavorable prognostic value. There may be terminal hyperpyrexia.

B. Special Characteristics in Cases Associated with Ethmoid Sinus Disease: Inflammatory disease of the ethmoid sinuses is so intimately bound up with disease of the sphenoid and frontal sinuses, and these so commonly occur together, that a separate discussion of this phase of nasal accessory sinus disease, so far as it concerns itself with secondary osteomyelitis of the skull, seems unnecessary. In the sense in which this communication is written, it seems probable that osteomyelitis of the skull occurs with least frequency after disease of the ethmoid sinuses, and then it is probable that associated disease of the frontal sinus exists.

In the cases of diseased ethmoid sinuses, perforations occur as follows: (a) into the orbit (an orbital phlegmon results) or (b) into the nasal cavity.

With disease of the ethmoid sinus, localized forms of osteomyelitis of the skull bones occur in which the process is more or less limited to the nasal process of the superior maxillary bone, the crista galli and cribriform plate of the ethmoid or the thin bony plates forming the mesial wall or roof of the orbit. In the cases of ethmoid sinus disease the general tendency is for the infection to spread forward and slightly upward in the directions just indicated, i. e., to the lacrimal bone, the nasal process of the superior maxillary bone, the cribriform plate and the crista galli.

Diffuse forms of cranial osteomyelitis do not occur, in my opinion, unless involvement of other sinus groups, especially the frontal, coexist.



The symptomatology of perforation in cases of ethmoid sinus disease is nil when the perforation occurs in the nasal cavities, except for some usually undervalued increase in the nasal discharge. There is a characteristic amelioration of the symptoms. In well marked cases of disease of the ethmoid sinus this should be suspected when these two characteristics are encountered.

In cases in which the perforation occurs into the orbit, the symptomatology is that characteristic of an orbital phlegmon, is sometimes more or less dramatic, and is frequently secondarily complicated by intracranial lesions.

Hubby's <sup>46</sup> case is a good illustration:

The postmortem examination showed: exophthalmos and pus in the orbit; left lateral sinus thrombosis; left sigmoid and left cavernous sinus thrombosis, but not purulent; necrosis of the wall of the right orbit. There was a one week's history, the infection having apparently begun in the nasal cavities.

C. Special Characteristics in Cases Associated with Sphenoid Sinus Disease: It is probable that cases of sphenoid sinus disease are frequently mistaken for other entities, and experiences are on record where the cases are confounded with disease centered in the frontal or ethmoid sinuses or with foci in the middle ear or mastoid. It seems certain from the reports in the literature that recognition of the development of an acute osteomyelitis in the body of the sphenoid rarely occurs during life; the diagnosis is apparently most commonly made at the postmortem examination.

Owing to this fact the number of cases reported in the literature do not reflect the actual numbers of cases that have undoubtedly occurred, nor the relative frequency to other types of nasal accessory sinus disease. Cases of sphenoid sinus infection usually find their way into the recorded literature because of the bizarre clinical picture; more especially because of the apparently sudden onset of a rapidly fatal illness, which is usually proved later to be but a hyperacute exacerbation of an old infection, and most especially because of the intracranial complications that occur, the apparently sudden appearance of which causes the alarming change in the clinical picture and furnishes these powerful elements that overwhelm the resistance of the patient and gives the fatal character to the illness. The rôle of any osteomyelitis is usually lost in the clinical turmoil.

In 1929, Kramer <sup>47</sup> could find less than a hundred cases of sphenoid sinus disease with complications in the literature. He reported nine cases of this kind from the Mount Sinai Hospital, five of which occurred in the hospital in the preceding year. Among these nine cases,

46. Hubby: *Laryngoscope* 31:204, 1921.

47. Kramer, Rudolph: *Laryngoscope* 39:573 (Sept.) 1929.

there were two in which frank osteomyelitis of the bone of the skull was present either as a coincidence in the total clinical picture, or as the means by virtue of which other intracranial complications had been brought about.

Kramer<sup>47</sup> supplied the notes of these cases:

A man, aged 50, had a cold in the chest for several weeks; for three days he had had fever; for two days he was restless, delirious, and finally unconscious. Physical examination showed: marked toxemia, signs of meningitis, bilateral early papilledema, vertical nystagmus, an enlarged heart and peripheral atherosclerosis. Lumbar puncture yielded purulent fluid under increased pressure containing pneumococcus type I. Death occurred two hours after admission.

Postmortem examination showed: diffuse meningitis, more marked at the base; right cavernous sinus phlebitis; pus in both posterior ethmoid and sphenoid sinuses; the body of the sphenoid sinus, hemorrhagic and purulent, and a red glazed pharynx and nasopharynx covered with dried purulent crusts. Pneumococcus type I was isolated in the aforementioned lesions.

A woman, aged 55, gave a history of symptoms of five months' duration, which followed a chronic course. There were intracranial manifestations. A diagnosis of a metastatic malignant condition was made at first because of coexistent lesions unrelated to the principal disease process. The examining rhinologist diagnosed sphenoiditis, and a bilateral operation was performed. The Friedländer bacillus was found in the spinal fluid and in the sinuses. After the intranasal operations, the patient was markedly relieved for two weeks, and the cells in the spinal fluid dropped from 2,400 to 175 and from 89 to 50 per cent polymorphonuclears. Meningitis developed. Intravenous therapy was instituted for sepsis. The patient went into a state of coma, and died.

Postmortem examination showed: purulent meningitis and encephalitis, a large left sphenoid sinus containing creamy, yellow pus and a right sphenoid containing a small amount of pus, as did the ethmoids on both sides. Posterior to the left sphenoid, the medulla of the basisphenoid and basiocciput was soft and friable, with a path of necrotic bone leading from the left sphenoid sinus through the basiocciput perforating into the cerebellar fossa. The dura here was perforated. The surrounding dura was thickened, dull in appearance and covered with pus. The pus was adherent over the perforated dura. A culture revealed atypical bacillus of the Friedländer group.

The pathway of infection was from the larger sphenoid sinus, through the medulla of the basisphenoid and basiocciput, through the dura of the cerebellar fossa and into the pia-arachnoid. There had been temporarily a successful attempt on the part of the meninges to wall off the process in the region of the necrotic cerebellar floor, but this barrier was finally broken down.

I have been able to find the following additional cases in the literature:

EAGLETON.<sup>48</sup>—The patient had had chronic "catarrh" of the nose and throat, bilateral chronic otitis and bilateral acute exacerbation of otitis media. Four weeks later double vision developed. There were general symptoms of general infection, and tenderness of the right mastoid. An intra-oral incision was made

<sup>48</sup> Eagleton, W. P.: Cavernous Sinus Thrombosis, New York, The Mac-Millan Company, 1926.

of an empyema of the sphenoid sinus pointing into the nasopharynx; bare bone was palpated extending upward into the base of the skull. Subsequent exploration and exenteration of the sphenoid and ethmoid sinuses were done. The patient died. Postmortem examination revealed thrombosis and suppuration in the right lateral sinus and jugular vein and bulb.

HOSTON.<sup>49</sup>—The patient suffered from pain over the eyes, purulent secretion from the nose, exophthalmos and paresis of the facial muscles. Death occurred.

The diagnosis made on section was inflammation of the sphenoidal sinus associated with osteomyelitis, necrosis and gangrene of the basilar sphenoid and occipital regions, thrombosis of the cavernous sinus and ethmoid; purulent meningitis, pulmonary abscess and parenchymatous degeneration in the viscera.

GRANT.<sup>50</sup>—In a fatal case of sphenoid osteomyelitis, at autopsy the sella turcica and body of the sphenoid were found to be brown and markedly soft and readily admitted the chisel. The entire body was similarly involved. The other bones were normal.

The postmortem diagnosis was: abscess of the body of the sphenoid, osteomyelitis of the sphenoid, basilar meningitis, cerebral edema, otitis media purulenta, bronchopneumonia, myocarditis, acute splenic tumor, acute glomerular nephritis and toxic nephrosis and passive congestion of the liver, spleen and lungs.

In the sphenoid sinus, perforation occurs as follows:

(a) Through the floor or anterior wall of the sphenoid and into the superior pharynx. An abscess forms between the bone and the mucous membrane of the roof of the pharynx.

(b) Through the roof of the sphenoid in the general neighborhood of the sella turcica. This leads immediately to certain intracranial complications (extradural abscess at the base of the skull, meningitis, sinus thrombosis), which will be discussed subsequently. An illustrative postmortem report is that of Key-Alberg:<sup>51</sup>

Postmortem examination showed the following: meningitis in the ventricles and in the subarachnoid cavities at the base, especially in the posterior cavum cranii. There was no exudate over the hemispheres. After removal of the infundibulum, an irregularly shaped lesion the size of a farthing was found to the right of the anterior wall of the sella turcica. This perforation had blood-stained edges, and opened into the sphenoidal cavity, which still contained a not inconsiderable quantity of pus, mixed with blood and coagulation. Thrombosis was present in the cavernous sinus on both sides and in the ophthalmic vein on the right side.

The pathologico-anatomic possibilities and the difficulties in diagnosis and in interpretation of the postmortem findings are well illustrated by one of the cases from Mount Sinai Hospital, reported by Kramer:<sup>47</sup>

A woman, aged 53, had a prodromal period of one month in which there was headache, continued nasal discharge, intermittent vomiting, pain in the back of the

49. Hoston: *Norsk. mag. f. lægevidensk.* 72:559, 1921.

50. Grant: *Laryngoscope* 41:842, 1931.

51. Key-Alberg: *Acta oto-laryng.* 3:37, 1921.

head, septic temperature for three days before admission, unconsciousness, and then coma. Death occurred twelve hours after admission.

Briefly summarized, postmortem examination showed pus in the left antrum and some of the ethmoid cells; the sphenoid sinus was absent. In the body of the sphenoid there was a sinus tract (possibility of craniopharyngeal sinus infection) 0.5 cm. in diameter, filled with detritus, which ran from the roof of the nasopharynx through the sphenoid bone in an upward and backward direction for a distance of 1.5 cm. The sella turcica was eroded, and the periosteum over the sphenoid bone at the base of the skull was considerably thickened, and in places it was lifted from the underlying bone. There were basilar meningitis, hypophysitis, ependymitis, purulent bronchopneumonia and an old tuberculous cavity.

The spread of an osteomyelitic process originating in the sphenoid occurs from the posterior part of the body of the sphenoid to the adjacent part of the basilar process of the occipital bone across the line of articulation. The physical basis for the extension in this direction and its limitation thereto lies in the occurrence of diploic tissue in this part of the sphenoid only, and in its continuation into the basilar portion of the occipital bone; diploic tissue is apparently absent in other parts of the sphenoid. Rarely, if ever, apparently, and for this reason, does the process extend outward into the wings of the sphenoid; I have seen no mention of this in the reported cases; in one case its absence is distinctly commented on (Grant<sup>50</sup>) in the postmortem protocol.

It is characteristic of osteomyelitis of the skull originating in the sphenoid that the process is always localized and is limited to the posterior part of the body of the sphenoid and the basilar portion of the occipital bone. Diffuse forms of osteomyelitis of the skull never occur from a sphenoid origin. The close proximity to the extremely important structures at the base of the brain, the great opportunity and facility for the transference of the infection to and within the meninges, the ease and readiness with which extradural abscess forms, all make for a rapid development of fatal intracranial lesions, which bring death before the osteomyelitis can spread to any great distance.

The symptomatology of cases of sphenoid perforation has certain characteristic features:

(a) Cases are reported by Eagleton<sup>48</sup> and others in which a tumefaction is palpated in the roof of the pharynx, which when opened is found to be referable to a perforation in the appropriate wall of the sphenoid. Undoubtedly this happens more often clinically and is not diagnosticated because practitioners do not often palpate the superior pharynx, and in any case the swellings are difficult to feel; spontaneous perforation then occurs. The latter is also commonly unrecognized owing to the fusion of the resultant discharge, after spontaneous perforation through the mucous membrane of the pharynx, with that from the natural opening of the sphenoid, from other sinus groups or from the general nasopharyngeal cavity.

(b) Occasionally the perforation is to one or the other side of the midline: suppuration then develops in the general neighborhood of the pterygomaxillary fossa. The latter conditions may be suspected, if, with distinguishable signs of sphenoid disease, difficulty and inhibition is present in the free use of the temporomaxillary articulation (opening of the jaws). Commonly this complication is unrecognized.

Except for a limited number of cases of this kind, it is not possible to distinguish any symptomatology inherently referable to any osteomyelitis at the base of the skull originating from the sphenoid, because the occurrence of the latter is invariably associated with intracranial complications, notably a basilar meningitis, the signs of which dominate the clinical picture. The diagnosis is to be made by inference only in the following circumstances:

(c) It seems correct to say that in cases of established or suspected sphenoid sinus disease, a sudden, acute, overwhelming exacerbation of symptoms, especially if these point to the basal meningeal areas, indicate a perforation in the roof of the sphenoid.

(d) A less dramatic and slower development of an intracranial lesion indicates the probable, though not the invariable, preexistence of an osteomyelitis. In general, it is to be said that in any patient with subjective and objective signs of sphenoid sinus disease, the occurrence of persistent headache and vomiting, and the development of the objective signs of meningeal irritation—stiffness of the neck, Kernig sign, etc.—should lead one to suspect that an intracranial lesion is developing, so that there is urgent need of immediate verification. Any more or less proved suspicion of the presence of an intracranial complication should immediately furnish the necessary criteria for the assumption that an osteomyelitis at the base of the skull originating in the sphenoid is probably present. The literature gives one the impression that neurologists have been more alert in making this diagnosis than the rhinologists.

Osteomyelitis of the sphenoid, because of the predilection for intracranial complications, especially purulent basilar meningitis, is apt to have (1) either a very acute and fulminant course with a fatality in a few days, or (2) a more chronic course lasting a month or more and ending most usually in death. Commonly the clinical course shows a combination of the two: a more or less prodromal period with obscure symptoms and physical signs, and then a sudden overwhelming of the body with fulminating infection, usually the expression of a terminal meningitis, which rapidly results in death.

A most important symptom in sphenoid sinus disease and in osteomyelitis of the base of the skull derived therefrom is pain in the head. Pain in the ear and mastoid regions occurring on both sides simultaneously in the absence of any objective signs of disease in those regions should lead one's attention to trouble at the base of the skull

in the region of the sphenoid. Even in the presence of disturbance in the mastoid regions, such pain has a certain amount of significance. Diffuse headache is also important. It sometimes begins in the frontal region and spreads to the occipital region; it then indicates involvement of the sphenoid region. When the headache becomes persistent and possibly of increasing severity, when it is difficult to control by the ordinary means and when it is associated with lethargy and, possibly with occasional vomiting, it becomes the most important single sign and symptom of the prodromal period in which osteomyelitis of the sphenoid bridges the chasm between sphenoid sinus disease and fatal intracranial complications.

Choked disk with optic neuritis is another important symptom of sphenoid disease. The discussion of this symptom beyond its bare mention is possibly beyond the scope of this paper.

#### OSTEOMYELITIS OF THE SKULL IN ASSOCIATION WITH ACUTE INFECTION OF THE TONSILS

The importance of the intercurrent of an additional acute infection in a subject in whom a preexisting sinus disease is present—especially sphenoid sinus disease—as a factor in the exacerbation of the sinus disease which leads to the occurrence of intracranial complications was pointed out and emphasized by Eagleton.<sup>45</sup>

There are references in the literature to cases of acute osteomyelitis of the base of the skull that have followed an acute infection of the tonsils, or have followed an operation on the tonsils and adenoids. As there is always present an older lesion in the nasal accessory sinuses, most usually in the sphenoid cells, Eagleton assumed that the acute infection in the tonsils or that following the operation on the tonsils and adenoids has brought about an acute exacerbation of the infection in the sinuses, and that the osteomyelitis of the skull owes its existence to the latter. The assumption seems most reasonable and is probably correct.

I have been able to find the following illustrative cases in the literature:

JACQUES AND LUCIEN.<sup>52</sup>—A peritonsillar abscess was present, which was opened. The ears were normal. A gangrenous osteomyelitis of the body of the sphenoid and the apex of the petrous bone developed. A cavernous sinus thrombosis followed. Death occurred in three days.

HOSTON.<sup>49</sup>—The symptoms started in the neck. There was pain when the patient opened his mouth. Death occurred in five days. Diagnosis on section was angina phlegmonosa, thrombosed cavernous sinus, osteomyelitis and necrosis of the sphenoid and occipital bones, purulent meningitis and edema of the meninges.

WYLIE.<sup>41</sup>—In a 48 year old woman acute tonsillitis developed, followed by a peritonsillar abscess. In the following sixteen days there was increasing swelling

52. Jacques and Lucien: Bull. et mém. Soc. franç. d'otol., May, 1908.

and proptosis of the left eyeball and much pain in the throat and back of the head. The abscess was incised. Two days later, the temperature was still elevated, and thick pus was escaping from the wound. Both eyes became swollen. Death followed.

Postmortem examination showed a large sloughing abscess, lateral and posterior to the pharynx, extending upward to the base of the skull in the prevertebral area, to a focus in the basiocciput and sphenoid. Meningitis and encephalitis were also present.

O'MALLEY.<sup>53</sup>—Three weeks after an operation on the tonsils and adenoids signs of a cavernous sinus thrombosis appeared, and the patient died soon thereafter. Postmortem examination showed, in addition, osteomyelitis of the body of the sphenoid.

O'Malley's experience was that in all cases of death from cavernous sinus thrombosis following tonsillectomy, the sphenoid was involved.

D. Special Characteristics in Cases Associated with Antral Disease: A good deal of confusion exists between the subjects of antral infection and osteomyelitis of the superior maxilla. It seems undoubted that either one can produce the other. In any event, extension of infection from the superior maxilla into the cranial bones, no matter what the etiology is, seems to be extremely rare. Communication with the cranium exists at the nasal process of the maxilla or through its ethmoidal connections; and it seems very probable when antral sinusitis is followed by an osteomyelitis of the skull, that other sinus groups, notably the frontal and ethmoid groups, are also involved. The following are illustrative cases:

SKILLERN.<sup>38</sup>—This case is an example of an extension of an osteomyelitis of the nasal process of the superior maxilla to the frontal bone and skull. It appears that pansinusitis existed, and osteomyelitis developed in the maxilla and spread on the one side to the frontal bone and, on the other, to the malar bone. The infection was due to *Staphylococcus aureus*.

HANSON.<sup>54</sup>—There was a left upper "abscessed" tooth, which was extracted. Foul suppuration was found in the left antrum, which was drained by osteotomy of the nasal and facial surfaces at the anterior inferior angle in front of and below the inferior turbinate bone. There was a recurrence of symptoms, and extension of the process upward; an incision was made over the left frontal sinus, and the diseased bone exposed. Sequestrums were removed from the frontal bone. Bacteriologic examination showed *Streptococcus hemolyticus*. The patient was lethargic, with signs of meningeal irritation, convulsions and stupor; then death followed. Postmortem examination was not made.

CONNER.<sup>55</sup>—A 38 year old man had suppurative maxillary sinusitis; the other sinuses apparently were not involved; drainage was obtained through the socket of the second upper left bicuspid and by enlarging the opening in the inferior meatus. A small infected lesion was present in the floor of the vestibule of the

53. O'Malley, in discussion on Davis: *Proc. Soc. Med. (Laryngol. Sect.)* 13:174, 1912.

54. Hanson: *U. S. Vet. Bur. M. Bull.* 6:241 (March) 1930.

55. Conner, W. H.: *U. S. Vet. Bur. M. Bull.* 5:417 (June) 1929.

left nostril. There was pain along the distribution of the left fifth nerve, and fever. A tender swelling developed in the region of the left lacrimal sac, increasing to cover the whole infra-orbital region. A roentgenogram showed no apparent involvement of the frontal sinus, but the swelling extended upward onto the forehead and to the opposite side of the nose. Incisions were made in the left cheek, the forehead and the right side of the nose; the periosteum was lifted; the bone was found inflamed, but there were no sequestrums. Bacteriologic examination showed streptococcus, Staphylococcus albus and Micrococcus catarrhalis. Culture of the blood gave negative results. There were signs of meningitis. The patient died.

The mechanism is apparently one of two: (1) extension of an osteomyelitic process in the maxilla through its nasal process into the frontal bone, or (2) as in other cases of frontal sinus disease, due to an associated frontal sinusitis.

The occurrence of osteomyelitis of the skull under either of these two conditions is rare.

*Extension from a Focus of Infection in the Otologic Apparatus.*—In discussing this phase of the subject of osteomyelitis of the skull, no attempt will be made to include the subject of middle ear or mastoid disease as customarily understood among internists and otologists, except where elucidation of the subject of cranial osteomyelitis demands it.

There is little in the literature concerning cranial osteomyelitis after middle ear and mastoid disease. This is encountered under two conditions: (1) as isolated and incomplete references to this association in the reports of cases of mastoid disease or (2) in larger communications dealing (a) with the subject of nasal accessory sinus disease and its complications, or (b) with the subject of cranial osteomyelitis. The sparsity of the literature is noteworthy because it calls attention to the actual small numbers of cases of cranial osteomyelitis that follow an otologic origin, and to the relative abundance of this complication after nasal accessory sinus disease as compared with its occurrence after middle ear and mastoid disease.

A report of 266 cases of streptococcic osteomyelitis of the temporal bone was made by Boyd-Snee<sup>56</sup> in 1922. A great many facts were given, out of which one can extricate the following: (1) It is always associated with a middle ear infection or with an exacerbation of it; (2) invasion occurs by continuity of structure or by hematogenous paths; (3) the streptococcus is always present; (4) the term used is "uncomplicated" osteomyelitis of the temporal bone, and (5) the mastoid is apparently uninvolved; (6) the symptomatology is that of mastoiditis; (7) the usual intracranial complications are likely to occur—thrombophlebitis, meningitis and brain abscess.

56. Boyd-Snee, H.: J. Indiana M. A. 15:147 (May) 1922.



In the discussion of Boyd-Snee's paper (Breitenbach, Bulson), there was not entire agreement with the conclusions of Boyd-Snee. There seems to be a strong possibility that many cases of unusually widespread mastoiditis might have been included in the 266 cases reported by Boyd-Snee.

Osteomyelitis of the skull complicating middle ear and mastoid disease is far rarer than is the same complication after nasal accessory sinus disease. This is due both to (a) the essential anatomic conditions and (b) to the character of the manipulations during operation for mastoid disease.

(a) The squamous portion of the temporal bone, the petrous pyramid, the zygoma, the adjacent parietal bone, and the occipital bone are the bony structures that are of most interest. In looking at an articulated skull, it is readily seen that the pneumatic portion of the temporal bone, which makes up the mastoid, is surrounded in the superior, anterior and posterior directions by a continuous area in which the diploe between the tables of the skull is at a minimum. In the flare of the squamous portion of the temporal bone the diploe is absent; some diploe is usually present in the root of the zygoma; anteriorly, where the bone articulates with the wings of the sphenoid, it increases somewhat in extent; toward the occipital bone, the cancellous structure begins to become prominent. Here, however, it will be noted that the pneumatic structure of the mastoid is accomplished by plates of dense bone, and no true diploe exists. Posteriorly, also, where the temporal bone articulates with the occipital bone, the lateral sinus is lodged, and the diploe practically does not exist as its potential space is occupied by the venous sinus.

At the periphery of the temporal bone, where the bone thickens out to articulate with its neighbors, diploic structure begins to appear (fig. 8). In adults, as was pointed out previously, when the articulations disappear, the venous plexus contained in this diploic structure becomes continuous with that of its neighboring bones, the parietal, the occipital and the greater wing of the sphenoid.

The petrous portion of the temporal bone is composed of dense hard bone. It contains the auditory apparatus and the labyrinth and several canals for the transmission of nerves and vascular channels. In spite of its traditional hardness, a certain amount of cancellous (diploic) structure is found scattered in the very hard dense bone which makes up the bulk of the petrous pyramid and which makes up the various walls of the auditory apparatus, the labyrinth and of the various channels. Even though the middle ear and the mastoid cells are so closely associated with the pyramid, this dense bone seems to wall off the latter chambers very effectually from the little diploic structure contained within it.

Toward the base of the skull the apex of the pyramid lies in association with the basilar process of the occipital bone; the relationship resembles accurately that between the posterior part of the body of the sphenoid and the basiocciput.

In operating for mastoid disease, the aim is to clear out all of the pneumatic portion. When the operation is efficiently done, the entire cavity resulting from the operation is bounded by dense bone, and the latter is a fairly efficient barrier to the transfer of any infection into the cranial diploe.

In association with otologic infection, the spread of the latter occurs in a number of directions. According to Neumann,<sup>57</sup> they are, in order of their frequency: (1) mastoid process, (2) fossa sigmoidea, (3) tegmen tympani et antri, (4) petrosa, including the labyrinth and

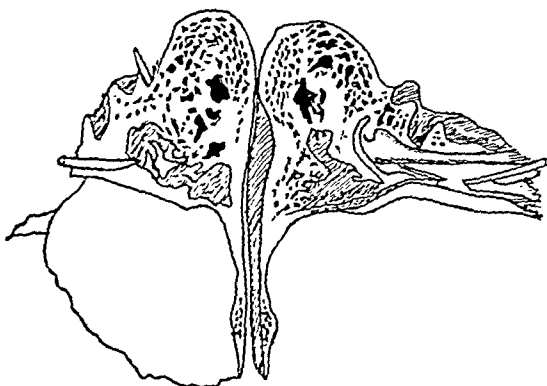


Fig. 8.—Cross-section of a temporal bone to show the relationship and distribution of the cancellous and hard bone.

(5) posterior limb of the external semicircular canal and the carotid canal. According to Druss,<sup>58</sup> from whom I am taking these facts and who gives the experience at the Mount Sinai otologic (Friesner) service, while the predilection for the cells of the petrous pyramid is fourth on the list, nevertheless, a petrositis is far more prevalent than was previously believed. This has been demonstrated both clinically and histologically.

The foci of osteomyelitis which are found in the skull in association with otologic infection occur, roughly, at the following sites:

(1) In the occipital bone. This is the commonest form, as when the infection spreads backward from the mastoid into the contiguous part of the occipital bone. It is usually interpreted as being an

57. Neumann, Heinrich: *Die otitische Kleinhirn-Abscess*, Vienna, Franz Deuticke, 1907.

58. Druss, J. G.: *Laryngoscope* 41:394 (June) 1931.

extraordinary extension of the mastoid cells, but in a certain number of these it is undoubted that there is a true extension into the diploe of the occipital bone. On the other hand, occipital involvement is extremely rare when a focus in the petrous pyramid spreads by contiguity to the basiocciput; this will be discussed subsequently in the section devoted to osteomyelitis in the pyramid.

(2) In the zygoma. This is possibly next in frequency, and is usually found at the root and in the body of the zygoma; it is also sometimes interpreted as being an extraordinary development of the mastoid cellular structure. The lesion tends to localize itself in a relatively small area, and being very close to the floor of the middle fossa, it is one of the varieties in which perforation is found to occur into the interior of the cranium and to give rise to extradural abscess and meningitis. Such a case was reported by Druss and Friesner<sup>59</sup> from Friesner's service at Mount Sinai Hospital:

A boy, 6 years old, had headache, pain in the left ear and spontaneous rupture of the drum. The symptoms continued. There were physical signs of meningitis. The spinal fluid contained meningococcus, and a blood culture was sterile. A roentgenogram of the mastoid area was negative. The boy was discharged with a diagnosis of meningococcus meningitis.

He was readmitted five months later with a seventeen day history of aural discharge, for which myringotomy was done. Twelve hours before admission, there were frontal headache and vomiting. The spinal fluid showed gram-positive cocci, which did not grow on culture. There was an increase in symptoms. Focal neurologic symptoms led to a diagnosis of temporosphenoidal abscess. The patient died.

Postmortem examination showed osteomyelitis of the inner aspect of the zygoma in the temporal bone and perforation of the bone through the adherent meninges. The remainder of the temporal bone was normal. There was a temporal lobe abscess.

(3) In the squama. The thinness of bone in this locality is proverbial, and various forms of subdural abscess and meningitis are described. An illustrative case is reported by Eagleton:<sup>48</sup>

The patient suffered from a deficiency in hearing. Sore throat developed, followed by increased diminution of hearing. Paracentesis was done to relieve the pain. The maxillary antrum was drained. After a right mastoidotomy the patient did well.

"Cold" developed, followed by pain on the top of the head. The mastoid wound suppurated. There were no meningeal symptoms; lumbar puncture revealed a sterile fluid. Operation showed extensive superficial necrosis of the squama just above the external auditory canal and zygoma, caries in the solid angle and serous meningitis. The sinus was free from disease.

Sepsis continued. Blood culture showed long chain streptococcus. The focus was found to be in the shoulder. Death occurred.

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59. Druss, J. G., and Friesner, I.: Pathways of Infection in Abscess of the Brain, *Arch. Otolaryng.* **13**:532 (April) 1931.

Postmortem examination showed thrombophlebitis of the right jugular vein and bulb, a carious condition of the base of the skull over the sphenoid extending into the basilar process of the occipital bone, serous meningitis with areas of exudation, pneumonia and pericarditis.

(4) In the petrous pyramid. Druss<sup>55</sup> studied these cases at Mount Sinai Hospital. Various paths have been described by Perkins,<sup>60</sup> Sears,<sup>61</sup> Chamberlain,<sup>62</sup> Maybaum<sup>63</sup> and others for the routes of extension of the infection from the middle ear and antrum to the pyramid. In the

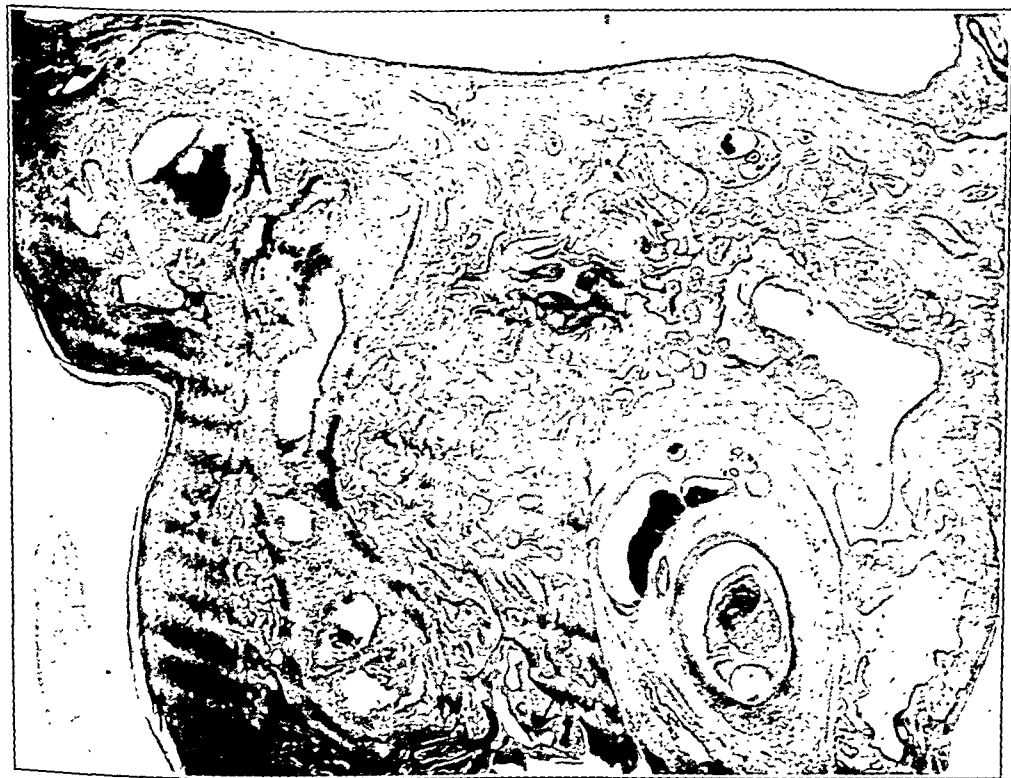


Fig. 9.—Low power picture from Druss' case showing at A the location of the abscess in the root of the zygoma. (Courtesy of Dr. Druss.)

main, they are along the paralabyrinthine cells (above, below and on the side of the labyrinth), along the cells accompanying the eustachian tube, through the carotid canal, through the subarcuate fossa, along the superior and inferior petrosal veins, from an extension of an extradural abscess or from a combination of these. As it spreads through the petrous

60. Perkins: *Ann. Otol.* **19**:692, 1910.

61. Sears: *Pennsylvania M. J.* **3**:844, 1910.

62. Chamberlain: *M. J.* **27**:566, 1924.

63. Maybaum, J. L.: *Laryngoscope* **30**:138, 1920.

pyramid, the infection may involve or avoid the labyrinth in its course. Other factors being equal, the more cellular the petrous pyramid, the more ideal is the situation for the spread of infection.

According to Druss,<sup>58</sup> the mastoid process, the petrous pyramid and the apex differ in their anatomic structure and in their pathologic picture. Usually the degree of infection is greater in the mastoid cells than in the paralabyrinthine cells, but the contrary may be true, and there may be little or no infection in the mastoid cells, and the paralabyrinthine cells or the cells at the apex may be the seat of a localized collection of pus. Such cases have been reported by Otto Mayer, Karlefore, Ulrich (quoted by Belinoff and Balan<sup>64</sup>) and others. Druss<sup>58</sup> demonstrated histologically that infection may subside in the middle ear and mastoid cavity but will increase in severity as it advances through the petrous pyramid. This bears out clinically the not too frequent occurrence of a dry, resolving middle ear associated with an intracranial complication.

These anatomic considerations give the physical basis (1) for the occurrence of osteomyelitis of the skull as a complication of middle ear and mastoid disease, (2) for its relative sparsity of numbers as compared with similar complications after nasal accessory sinus disease, (3) for the essential similarity of the clinical symptom complex and course and for similar associations with similar groups of intracranial complications.

The anatomic considerations outlined here give the physical basis for the very much lessened likelihood, which exists in otologic conditions necessitating mastoidectomy, of direct infection of the cranial diploe during the manipulations and steps of the operation. Unless the diploe is unusually well developed and extends well into and toward the field of a mastoid operation, it is difficult to understand how direct infection could mechanically be implanted into the diploe.

The following types of lesions are found:

(1) Perforations. These are unusual. The cases at Mount Sinai Hospital included only one of these in which the perforation occurred in the neighborhood of the root of the zygoma. Theoretically, perforations ought to be found with disease in the squama.

(2) Localized lesions. These form the bulk of the lesions found. Their localizations and physical appearances have been sufficiently indicated in the previous paragraphs. Practically all the remarks made here concern the localized type of disease.

(3) Diffuse lesions. There are no cases of this kind in the records at Mount Sinai. When I speak to otologists about this type of lesion, every one is of the belief that they are very rare; and no one, when

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64. Belinoff and Balan: Monatschr. f. Ohrenh. 64:1185, 1930.

actually pressed for an example, can give me a specific instance of this kind. I have a slight recollection of having seen mention of such an experience in the literature, but I am unable to remember where and under what condition. I get the distinct impression that diffuse cases of osteomyelitis of the skull are extremely uncommon after otologic and mastoid disease.

The sequence of events, when the osteomyelitis of the skull has an otologic origin, is, for practical purposes, exactly similar to that complicating nasal accessory sinus disease. Both of these sets of organs are hollow chambers, either of a simple or of a complicated outline, lined by mucous membrane and subject to the same type of infection produced in similar ways; indeed, in many cases there is a "pansinusitis," all of the accessory structures that communicate with the nasopharynx being included in this term. The bacteriology is similar; the essential pathology is similar, and the mechanism of production and the progression of the lesion is similar.

The relative sparsity of cases of cranial osteomyelitis after an otologic origin is explained by the relatively efficient way in which the area of primary infection—middle ear and mastoid—is walled off from connection with the general cranial diploe and with the relative sparsity of diploe which exists in that part of the skull immediately adjacent to the primary area. Probably in those cases in which the osteomyelitis of the skull develops, the diploe is extraordinarily well developed and reaches downward toward the area of primary infection to a greater extent than is usual. Given a similar origin, with similar organisms and similar pathogenesis and pathologico-anatomic lesions, it is to be expected that the clinical course will be similar in both types of cases—in those with origins in the nasal accessory sinuses and in the otologic area. For this very good reason, no attempt will be made to describe these aspects of the subject, as it will only necessitate repeating what was said in the part of this communication dealing with cases of osteomyelitis of the skull after nasal accessory sinus disease.

Exactly similar considerations apply with equal force to the various intracranial complications that occur—to their variety, to their pathogenesis, to their clinical course, to their treatment and to the final outcome.

Frey<sup>65</sup> has attempted to differentiate cases of ordinary middle ear and mastoid disease from cases of osteomyelitis of the temporal bone unassociated with otologic infection. His differential diagnosis depends on the following criteria: (1) particularly rapid development of the manifestations; (2) rapid deterioration of the general condition from the beginning with high temperatures, prostration, anorexia and rest-

65. Frey, G.: *J. Laryng. & Otol.* 40:308 (May) 1925.

lessness; (3) the presence of a retro-auricular swelling with especial reference to its early appearance, size and its tendency to extend rapidly beyond the mastoid limits; (4) the virulence of the infection; (5) frequency of involvement of the facial nerve and of disturbances of the vestibular apparatus; (6) the operative appearances: (a) the tendency to necrosis, (b) the presence of foci close by in the zygoma, squama or pyramid, or at a distance by way of the diploic veins; (7) rapid progress of the disease, and (8) involvement of other than the lateral sinus. Frey cited the following case:

A boy, aged 4 years, had a retro-auricular swelling behind and below the mastoid and extending to the occiput and into the muscles of the neck. At operation there was widespread necrosis, and the osteitis was found to extend into the spongy cancellous tissue of the zygoma and the occipital bone. A thrombosis of the lateral sinus with a surrounding abscess was present also.

Four days after operation, there was present chemosis of the upper eyelids and exophthalmos; the temperature was 105 F. The spinal fluid was negative; blood culture was sterile, and bacteriologic examination of the pus showed staphylococcus. Eight days later jaundice developed, and death occurred.

I have no doubt that cases of osteomyelitis of the temporal bone of this type—and most probably they are of hematogenous origin—occur from time to time. The chances are good that these differentiating criteria which Frey proposes are sound, and they are confirmed by Wittmack;<sup>66</sup> but it would take exceptionally sound and clever clinical sense to make the differentiation unless evidence of a hematogenous infection in general is undoubted and beyond question. One of the points that would carry weight with me would be the presence of *Staphylococcus aureus* as the provocative and etiologic organism for the infection.

A group of cases occur in which a focus develops in the petrous portion of the temporal bone and in which there is either no evidence of preceding middle ear disease or of mastoid involvement, or in which the middle ear alone is involved; sometimes the middle ear manifestations appear some time after the evidences of pyramid disease. In these cases the discussion always centers around the question of hematogenous infection. My own impression is that many of these are of hematogenous origin. There have been several such instances in the otologic service at the hospital, but usually the available data is somewhat insufficient to enable one to make an incontrovertible opinion. A pertinent case is the following:

A 62 year old colored man entered the hospital (service of Dr. Bachr and Dr. Freisner) with an unimportant history except for occasional gas pains during

66. Wittmack, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926.

the past three or four years. His present illness began four weeks before admission with an initial shaking chill followed by attacks of pain in the lower aspect of the left side of the chest, not increased by respiration, and accompanied by continued high temperature and daily severe chills. Physical examination revealed an acutely ill man with some impaired mobility of the left leaf of the diaphragm, bilateral costovertebral tenderness, more marked on the right, and marked tenderness over the liver. Blood pressure was 130 systolic and 90 diastolic. Hemoglobin was 82 per cent, the white blood count, 22,000 with 86 per cent polymorphonuclears. The Pirquet test was positive.

This clinical course continued in the hospital, and a week after admission a complete exploratory laparotomy was done, but nothing abnormal was found. The wound healed by primary union.

The course continued septic. The Wassermann test was negative. Blood cultures were persistently negative. Agglutination tests for typhoid and melitensis were negative. A search for malarial parasites revealed nothing. Prostatic smear revealed some pus cells but no organisms. Roentgenograms of the chest on two occasions were negative. Roentgen examination of the stomach and duodenum gave negative results. Normal urine persisted throughout the patient's stay in the hospital, and an intravenous pyelogram, taken to rule out some kidney infection such as a carbuncle, also revealed nothing. A leukocytosis of from 20,000 to 30,000 white cells with a polynucleosis of 90 per cent persisted. The general condition of the patient gradually deteriorated, and the only physical sign obtainable after operation was persistent marked tenderness over the liver.

Three weeks after admission, aspiration of the liver was performed. No organisms were obtained, and culture was negative. On the same day, following the aspiration, the patient had a severe shaking chill and a rise in temperature to 104 F. Examination shortly thereafter revealed definite signs of meningeal irritation; a spinal tap was performed, cloudy fluid being obtained that contained 4,000 cells and 76 per cent polymorphonuclear cells; smear and culture of the latter were negative. Daily examination of both ears revealed no changes. The sepsis and the meningeal signs remained unchanged, and the spinal fluid gradually improved; about eight days later the latter was clear and contained only 12 cells. The next day a thick discharge developed from the right ear; the ear drum was flat anteriorly, and only a small amount of fairly thick discharge was present in the inferior sulcus; smear and culture of this pus revealed a pneumococcus type III. A roentgenogram of the mastoids was negative.

Two days after the ear began to discharge, a spinal tap was again taken and revealed a cloudy fluid with 2,500 cells, 78 per cent of which were polymorphonuclear cells. A terminal bronchopneumonia preceded death about forty-eight hours later.

Postmortem examination revealed: chronic purulent osteomyelitis of the petrous portion of the temporal bone (right) with bone abscess, acute purulent basilar meningitis, carbuncle of the left suprarenal with suppuration of the posterior wall of the lesser sac and phlebitis of the splenic vein, thrombophlebitis of the portal vein with phlegmonous suppuration of the liver, bronchopneumonia of both lower lobes of the lungs, acute purulent bronchitis, parenchymatous degeneration of the viscera, acute congestion of the lungs and the liver, atherosclerosis with calcification of the aorta, hypertrophy of the left ventricle of the heart, and cysts of the kidneys.

The notes of the case are deficient in very valuable and pertinent bacteriologic data. Nevertheless, it seems evident that this entire



clinical entity is a hematogenous general infection with undemonstrable bacteremia in which metastatic foci were present in the suprarenal gland (a carbuncle) and in the petrous portion of the temporal bone. This opinion is concurred in by the otologic department at Mount Sinai Hospital (Friesner), and by the medical department (Dr. Baehr).

There is a marked clinical similarity between disease of the pyramid and of the sphenoid bone. Both of these lie in the same anatomic position with reference to the base of the skull and the adjoining intracranial structures. Perforations occur in the pyramid as well as in the sphenoid, and there is the same predilection for extradural abscess and meningitis; brain abscess also occurs. A characteristic symptom complex for pyramid disease is Gradenigo's syndrome—involvement of the gasserian ganglion and of the abducent nerve; but as the syndrome has been found to occur without bone change, the connection is not absolute.

The intimate associations between the petrous pyramid and the sphenoid bone is well illustrated in the case reported by Gelanze:<sup>67</sup>

In this patient there was a ten years' history of a chronic otorrhea and chronic otitis media which followed an influenza. The present recrudescence began two months before admission with pain, fever, increased discharge, considerable retroauricular swelling and the physical signs of meningitis, including turbid lumbar fluid. A mastoid operation was done, and following this the manifestations diminished.

One week before death the symptoms reappeared with increased meningeal signs. The local mastoid wound and the middle ear were not in satisfactory shape (fungous granulations, cholesteatomas), and there was necrotic and sequestering bone. The symptoms increased, and facial paralysis developed. There was a sudden aggravation of symptoms followed by death.

The postmortem anatomic diagnosis was seropurulent meningitis of the left temporal and cerebellar fossa; necrosis of the petrous bone, the sphenoid bone and the sella turcica, with perihypophysitis.

On careful study of this case, I agree with Gelanze<sup>67</sup> that the infectious process, produced by germs of considerable virulence with a marked necrotizing power, had in the first place attacked the meninges through the tegmen antri, giving rise to meningitis which was promptly circumscribed by the local reaction. In spite of the rather extensive mastoid evacuation at the first operation, the osteomyelitic process became promptly propagated to the perilabyrinthine cells and to the labyrinth itself, thus permitting the germs again to attack the cerebellar fossa by way of the saccus endolymphaticus and to give rise to a new meningitic process. At the same time, in spite of the second intervention, and the complete petrotympanic evacuation, the necrotizing osteomyelitic process rapidly advanced toward the petrous bone and after only two days resulted in sequestration of the entire facial segment.

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67. Gelanze, C.: Valsalva 6:86, 1930.

followed by paralysis of the facial nerve; the entire acoustico-vestibular nerve bundles underwent necrosis. On reaching the extreme mesial limit of the petrous bone, the osteomyelitis by way of the periosteal vessels and lymphatics next attacked the body of the sphenoid bone and became diffused to the sella turcica, giving rise by its vicinity to a perihypophysitis which remained without evident clinical symptoms. The extension of the necrotic process and the considerable absorption of the toxic substances produced in large amounts in the infectious focus were the principal causes of the patient's death.

I have been able to find the following additional cases of osteomyelitis of the skull of otologic origin reported by various authors in the literature:

HUNTER TODD.<sup>68</sup>—A 53 year old woman had middle ear and mastoid disease; during mastoidectomy, an area of osteomyelitis was exposed behind the mastoid extending into the occipital bone as large as the palm of one's hand. There was secondary spontaneous sequestration of necrotic bone from the occipital area. Later recrudescence of symptoms occurred over the parietal bone with operative revision of the wounds and new areas. There was a period of partial remission with recrudescence of symptoms. The patient's condition followed a gradual downward course until death. Postmortem examination showed the typical wormeaten appearance of the cranial bones with areas where the bone was absent (sequestered areas).

HARRISON.<sup>69</sup>—A 25 year old man had middle ear and mastoid disease; radical mastoidectomy was followed by septic type of temperature. On revision of the wound thrombophlebitis of the lateral sinus was found. The symptoms continued. There were subperiosteal abscess over the squamous portion of the temporal bone, spontaneous sequestration and numerous abscesses under the scalp. The patient was operated on twenty times, with recovery.

GRUNWALD.<sup>70</sup>—A 63 year old man had middle ear and mastoid disease; at mastoidectomy, no pus was found, but the cells contained granulations. Later, an abscess in the posterior triangle of the neck was incised and drained. There was retention of pus. On revision bare bone was felt in the occipital region. Secondary revision was done with removal of the occipital bone as far as the inferior nuchal line, the seat of a necrotizing osteomyelitis.

PRATT.<sup>71</sup>—A boy of 5 years had a purulent middle ear disease; the mastoid was explored because of stiffness of the neck and a turbid spinal fluid containing hemolytic streptococci. Revision was done because the patient's condition did not improve. The intracranial contents were explored at this time with negative results. The patient died. Postmortem examination showed necrosis of the anterosuperior part of the petrous pyramid, and meningitis.

EAGLETON.<sup>48</sup>—The patient suffered from alcoholic periodic insanity. There was infection of the upper respiratory tract with severe pain in the head; on the following day a stiff neck and pain in both ears developed. There was hogginess

68. Todd, quoted by Luc (footnote 5).

69. Harrison: *J. Laryng., Rhin. & Otol.* 27:628, 1912.

70. Grunwald: *Ztschr. f. Hals-, Nasen- u. Ohrenh.* 2:139, 1922.

71. Pratt, E. L.: *Laryngoscope* 38:409 (June) 1928.

over the mastoids. The patient had a high temperature, a cough, and was delirious and irrational. Two blood cultures were negative. Aural culture showed diplococcus. The right mastoid was explored, showing an abscess in the suboccipital region from suppurative osteomyelitis of the occipital bone and pus in the right mastoid. An antemortem blood culture (four hours) revealed streptococcus. Death occurred.

Postmortem examination showed: suppuration of the sphenoid sinus; occipital edema; superficial abscess below the mastoid; deep abscess in relation to the upper four cervical vertebrae; purulent thrombophlebitis of the right lateral sinus extending to the torcular and into the jugular veins, involving the right superior and inferior petrosal, cavernous and anterior and posterior circular veins. The left cavernous sinus and the superior longitudinal sinus were also involved. Other findings were incidental to the general infection in the viscera.

EAGLETON.<sup>48</sup>—The patient had a left chronic otitis media with acute exacerbation, accompanied with chills and fever (107 F.). Mastoidectomy revealed sclerosed bone and thrombophlebitis of the lateral sinus. Blood culture was negative. The septic type of temperature continued followed by operation on the jugular bulb (Grunert's operation); there was no bleeding from the inferior petrosal sinus. A blood transfusion was done. A second blood culture was negative. Lumbar puncture revealed the fluid under slight pressure, with a cell count of 28; the globulin was slightly increased; Fehling's solution was reduced. No organisms were present. The symptoms continued, and death occurred.

Postmortem examination showed marked jaundice, a small extradural abscess of the posterior surface of the left petrous bone, with a local area of necrosis near the posterior semicircular canal, the dura being separated from the bone; a suppurating jugular bulb and pus in the left lateral sinus extending to the torcular vein; thrombosis of the left superior and inferior petrosal veins; right cavernous sinus thrombosis, and thrombosis of the basilar plexus and anterior spinal veins passing through the foramen magnum.

### ROENTGENOGRAPHIC EVIDENCE IN OSTEOMYELITIS OF THE SKULL

Roentgenographic evidence of osteomyelitis of the skull, when once the lesion is established, is generally similar for all classes and varieties of cases no matter what the etiology or pathogenesis. This, as is generally true in all cases of osteomyelitis, is not available at the beginning of the development of the lesion but appears relatively late. The evidence is available under two conditions:

(1). In localized forms of disease. This is especially well demonstrable in the osteomyelitis that accompanies frontal sinus disease, and takes the form of well demarcated sequestrations.

(2). In the diffuse variety. There is a characteristic moth-eaten appearance of the bones of the skull.

Roentgenographic evidence is especially demonstrable and available with lesions in the vault. Lesions at the base of the skull, no matter what their roentgenographic morphology may be, are not demonstrable at all or are demonstrable with extreme difficulty; for this reason well demarcated lesions which occasionally occur in the ethmoid are not recognizable.

Associated and indirect roentgenographic evidence of osteomyelitis of the skull is available only in the class of lesion associated with nasal accessory sinus disease, and is produced by the sinusitis per se.

According to Pfahler,<sup>72</sup> the roentgenologic signs of deep perisinusitis or changes incident to chronic ethmoid-sphenoid sinusitis consist in a cloudiness with a vague shading off of the anatomic details, thickening of the posterior and lateral wall of the sphenoid and ethmoid sinuses and an area of increased density which indicates osteitis of the surrounding bone.

This perisinusitis commonly extends into the middle fossa of the skull, but may involve also the petrous and mastoid portions of the temporal bones and even the posterior fossa. In some cases it is general and involves the base of the skull, but in others is confined to the side in which there is a deep sinusitis. Therefore, the conclusion may be drawn that it is an extension of the inflammation directly from the affected sinus. Pfahler<sup>72</sup> suggests that an effect on the sella turcica resulting from an extension of the inflammatory process may account for unexplained anomalies that have been observed by roentgenologists for many years.

#### OCCURRENCE OF GENERAL INFECTION IN OSTEO-MYELITIS OF THE SKULL

Cases with clinical signs of a general infection can be found in each of the pathologic and clinical groups outlined in this paper as follows:

(a) As the original general infection to which the skull lesion is a metastatic lesion.

(b) As a result of a primary infection of the bone tissue of the skull in civil or military injuries.

(c) As a secondary phenomenon in extension cases of osteomyelitis of the skull.

(d) Accompanying intracranial complications, especially meningitis and sinus thrombosis.

The number of cases in which positive blood cultivations are obtained are relatively few considering the total number of cases of osteomyelitis of the skull that have occurred, but are relatively large when intracranial complications are present. Even in these cases, however, the numbers of positive blood cultivations are not as numerous as one might suppose, and in the cases from Mount Sinai Hospital a positive blood culture was secured in one case only.

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72. Pfahler, G. E.: Roentgenologic Signs Which Indicate Extension of Infection from the Ethmoid and Sphenoid Sinuses to the Base of the Skull. *Arch. Otolaryng.* 8:638 (Dec.) 1928.

On the other hand, the numbers of cases in which there are undoubted clinical evidences of a general infection of the body, but in which the blood cultivations remain sterile, are relatively large, both in uncomplicated and in complicated osteomyelitis of the skull. Fatalities are very common in this group both because of the progressive nature of the local lesion and the occurrence of intracranial complications, as a consequence of the devastating effects of both of these two elements, and because of the general infection as evidenced by distant metastases.

### COMPLICATIONS

In cases of general blood infection (sepsis, septicemia, etc.), metastatic lesions are found post mortem in the various organs of the body; they are especially common in the kidneys, the liver and the lungs. I have encountered no mention of an endocardial lesion in cases of general infection of this kind (i. e., cranial osteomyelitis) in the literature. As was mentioned previously, the relatively uncommon occurrence of a general infection makes the finding of such metastatic lesions an equally infrequent one in clinical practice. Metastatic lesions such as these (i. e., in the kidney, liver, lungs) give no dominating picture and are commonly lost in the general symptomatology, both subjective and objective, of the clinical picture.

Cases of osteomyelitis of the skull, no matter what the provocative etiology is, are likely to be complicated by similar conditions, once they are fully developed; this is especially true when the infection has reached into the diploic venous system. Localized abscess formation is a relatively common complication.

### TYPES OF ABSCESES AND COMPLICATIONS

*Single or Multiple Abscess.*—These abscesses are subperiosteal (subepicranial). At first confined below the epicranium, they quickly cause a dissolution of this membrane, after which they spread in the subcutaneous tissues of the scalp. In cases of multiple abscess there may be appreciable separating distances between the various localizations.

This variety of abscess is relatively uncommon in traumatic primary cases of osteomyelitis of the skull. It is very common in hematogenous cases and in extension cases derived from disease of the nasal accessory sinus; it is less common in ethmoid sinus disease and otologic cases, and does not occur in cases of cranial osteomyelitis derived from sphenoid sinus disease.

*Extradural Abscess.*—This abscess is the intracranial counterpart of the external abscess just described. It, too, is a subperiosteal abscess situated between the dura and the internal table of the skull. Its more complete discussion is reserved for the section devoted to intracranial complications.

In the individual clinical and pathologico-anatomic groupings outlined in this communication, other forms of localized abscess formation appear. They are as follows:

*Orbital Abscess and Phlegmon.*—These abscesses are apparently more common than the intracranial complications which they frequently precede. There seems little doubt that the majority of intra-orbital inflammatory conditions owe their origin to nasal accessory sinus disease, and in most of these the essential intervening link is osteomyelitis. The complication occurs most commonly in diseases of the ethmoid and the frontal sinuses as a direct complication, and in roundabout ways (i. e., by way of a thrombophlebitis in the vascular channels, especially in the ophthalmic veins) in cases of sphenoid sinus disease. Orbital abscess does not occur in the otologic cases.

Birch-Hirschfeld's <sup>73</sup> experience is that 60 per cent of orbital inflammatory conditions are due to nasal accessory sinus disease. Kuhnt thinks this percentage is too low.

The mechanism is as follows:

(a) By perforation through the bony wall. This is especially common in diseases of the frontal and ethmoid sinuses.

(b) By direct extension of the process through some natural opening—optic foramen, superior orbital fissure, etc.

The autopsy on a patient of Leegaards <sup>74</sup> showed pus in the sphenoidal sinus, in the orbit, around the first branch of the trigeminal and around the chiasm.

(c) By thrombosis of the ophthalmic veins. An illustrative case is the following:

The autopsy in Vail's <sup>75</sup> case showed: chronic sphenoidal suppuration (right), necrosis of the orbital wall of the sphenoid, orbital phlegmon and suppurative phlebitis of the ophthalmic vein, the cavernous sinus, etc.

Additional forms of localized abscess formation occur in the cases of osteomyelitis derived from sphenoid sinus disease.

*Abscess in the Roof of the Nasopharynx.*—This abscess is a variety of, and a frequent predecessor of, frank retropharyngeal abscess. As pointed out previously, this can be palpated in the roof and in the posterior wall of the nasopharynx.

*Abscess in the Pterygomaxillary Fossa.*—These abscesses most commonly develop as a result of suppurative conditions in the base of the skull associated with sphenoidal disease, and are usually associated with

73. Birch-Hirschfeld, A.: *Vers. deutsch Naturf. u. Aerzte* 9:17, 1908.

74. Leegaards: *Acta oto-laryng.* 1:343, 1918.

75. Vail: *Laryngoscope* 29:263, 1919.

thrombophlebitis of the veins coming from the cavernous sinus and passing into the superior nasopharynx.

*Abscess in the Stylomaxillary Fossa.*—This abscess is a subvariety of pterygomaxillary abscess, and is especially common in those cases of sphenoid sinus disease in which a tonsillitis or a tonsillectomy has precipitated the clinical picture. The path of infection lies in the venous plexus of the carotid canal. The abscess may point in the neck below the angle of the jaw.

*Subperiosteal Abscess in the General Region of the Superior Aspect of the Spheno-Basiocciput.*—This type is specifically mentioned as a variety of extradural abscess which occurs with osteomyelitis of the skull derived almost exclusively from sphenoid sinus disease, and in relatively rare instances from an osteomyelitis of the apex of the petrous pyramid. It is the intervening link between bone disease in these localities and other intracranial complications (meningitis, venous sinus thrombosis, etc.), which will be discussed subsequently.

*Intracranial Complications.*—Osteomyelitis of the skull is especially noted for the occurrence of intracranial complications. In the twenty-nine cases of osteomyelitis of the skull compiled by Gerber, there developed:

Pachymeningitis	4 times
Extradural abscess	11 times
Intradural abscess	1 time
Thrombophlebitis	5 times
Cerebral abscess	4 times
Meningitis	9 times
Meningo-encephalitis (one septic)	3 times

In 1895, Kuhnt,<sup>76</sup> in his work on the frontal sinus, collected seventeen cases of intracranial complication associated with suppuration in that cavity. In twelve of these the frontal sinus only was diseased, while in the remaining five there was associated suppuration in other accessory cavities. Dreyfuss, in his monograph published in 1896, reported nineteen cases of a like nature following frontal sinus suppuration. The latter, however, are not to be regarded as being all additional to those reported by Kuhnt.<sup>76</sup> Killian, in his article on the frontal sinus in Heymann's "Handbuch der Laryngologie," published in 1900, brings the total number of frontal sinus complications up to thirty. Since that date, Turner has been able to add twelve additional cases not included in the statistics of the aforementioned writers, making the total number forty-two.

<sup>76</sup> Kuhnt, Herman: Ueber die entzündlichen Erkrankungen der Stirnhöhlen. Wiesbaden, J. F. Bergmann, 1895.

According to Turner,<sup>36</sup> the postmortem evidence of intracranial infection is somewhat meager. Newton Pitt,<sup>77</sup> who gives an analysis of 9,000 autopsies, found only one case of cerebral abscess due to nasal suppuration; the patient had had nasal polypi and ethmoid disease. Gowers<sup>78</sup> considers that chronic nasal disease is an occasional but rare cause of cerebral abscess. He stated that in 240 instances of brain abscess, the nose was the primary seat of infection in six, but the sinuses implicated are not specified. Treitel<sup>79</sup> found in 6,000 postmortem examinations three cases in which the intracranial mischief had its origin in the nose, namely, two of cerebral abscess and one with purulent meningitis. Wertheim<sup>39</sup> had access to the records of 10,394 autopsies; among these were 127 cases of endocranial suppuration. Fourteen were stated to be of nasal origin, but in six only was the exact mode of infection specified. In only three of these, again, was the frontal sinus the probable primary source of the complication.

This was the status in 1905, when Turner<sup>36</sup> published his paper. Since then a good many observations have been published, and the experiences of men like Eagleton have been particularly valuable. As a matter of fact, most of these observations are published because of the intracranial complications, and a considerable literature dealing with the latter has grown. One obtains the impression that intracranial complications occur most commonly with osteomyelitis of the skull derived from sphenoid sinus disease; the same situation exists with cases of osteomyelitis in the petrous pyramid, except for the great rarity of cases arising from this source. As a matter of fact, one might almost say that osteomyelitis of the spheno-basiocciput or of the petrous pyramid is so anatomically situated as to almost compel, if not invite, intracranial complications. Cases derived from foci of infection in the frontal or ethmoid groups of nasal accessory sinuses do not so readily lend themselves to the occurrence of intracranial complications: this is also due to anatomic considerations associated with the vault of the skull as opposed to the more intimate relationships at the base; but even here, when once the slowness of development, characteristic of many of the cases of cranial osteomyelitis derived from the frontal and ethmoid groups of sinuses, is lost, and the rapidly developing diffuse form of osteomyelitis is present, disparity of any kind between these two clinical groups disappears.

There are some differences of opinion as to the relative frequency with which intracranial complications occur in the group of cases of osteomyelitis of the skull associated with nasal accessory sinus disease

77. Pitt, Newton: *Brit. M. J.* 1:643, 1930.

78. Gowers, W. R.: *A Manual of Diseases of the Nervous System*, ed. 2, London, J. & A. Churchill, 1892.

79. Treitel, L.: *Berl. klin. Wchnschr.*, 1896, no. 51.



I think that some confusion exists in that it is not clearly stated whether the individual opinions refer to "nasal accessory disease" or to the "cranial osteomyelitis" which complicates the latter. I am inclined to agree with Burger that the majority of endocranial complications after nasal accessory sinus disease occur through the mediation of an osteitis of the bones housing the sinuses and of their continuations into the neighboring flat cranial bones. According to Burger,<sup>28</sup> this is based on operative and autopsy experience. Dreyfuss<sup>80</sup> found this status in twelve of nineteen cases in relation to the frontal sinus. Gerber<sup>26</sup> is very outspoken in his belief that almost every endocranial complication has its origin in infection of the bony wall.

**Mechanism of Development:** The mechanism for the development of the intracranial complications of osteomyelitis of the skull is almost purely a vascular one, and the infection is transmitted along the venous channels.

There are two main vascular channels.

(a) The transmission of the infection occurs through the anastomoses between the veins of the diploe and the veins of the dura. According to Gray:

These vessels communicate, in the interior of the cranium, with the meningeal veins and with the sinuses of the dura mater, and on the exterior of the skull with the veins of the pericranium and of the scalp. They are divided into the frontal, which opens into the supra-orbital vein by an aperture in the supra-orbital notch; the anterior temporal, which is confined chiefly to the frontal bone, and opens into one of the deep temporal veins, after escaping by an aperture in the great wing of the sphenoid; the posterior temporal, which is confined to the parietal bone, and terminates in the lateral sinus by an aperture at the posterior inferior angle of the parietal bone; and the occipital, the largest of the four, which is confined to the occipital bone, and opens either into the occipital vein or internally into the lateral sinus or torcular Herophili.

(b) By way of the emissary veins. According to Gray:

The emissary veins are vessels which pass through apertures in the cranial wall and establish communications between the sinuses inside the skull and the veins external to it. Some of these are always present, others only occasionally so. They vary much in size in different individuals. The principal emissary veins are the following: (a) A vein, almost always present which passes through the mastoid foramen and connects the lateral sinus with the posterior auricular or with an occipital vein. (b) A vein which passes through the parietal foramen and connects the superior longitudinal sinus with the veins of the scalp. (c) A plexus of minute veins which pass through the anterior condyloid foramen and connect the occipital sinus with the vertebral vein and deep veins of the neck. (d) An inconstant vein which passes through the posterior condyloid foramen and connects the lateral sinus with the deep veins of the neck. (e) One or two

80. Dreyfuss: *Sammelreferat*, *Ztschr. f. Ohrenh.*, 1908, vol. 103; quoted by Turner: *Edinburgh M. J.* 17:231, 1905.

small veins which pass through the foramen lacerum medium and connect the cavernous sinus with the pterygoid and pharyngeal plexuses. (f) Two or three small veins which pass through the foramen lacerum medium and connect the cavernous sinus with the pterygoid and pharyngeal plexuses. (g) There is sometimes a small vein passing through the foramen of Vesalius connecting the same parts. (h) A plexus of veins passing through the carotid canal and connecting the cavernous sinus with the internal jugular vein.

Besides these two main groups of channels, others are present as, for instance, the communication of the angular and supra-orbital veins with the ophthalmic veins at the inner angle of the orbit.

The various forms of extradural abscess are commonly infections by contiguity. The various forms of arachnoiditis, meningitis and venous sinus thromboses occur because of their contiguity to an inflammatory focus in the bone plus the extension of a thrombotic process along the vascular channels indicated.

Brain abscess is particularly prone to be a lymphatic condition. Perivascular lymphatics are especially found in connection with the vessels of the brain. The latter are enclosed in a sheath, which acts as a lymphatic channel, through which lymph is carried into the sub-arachnoid and subdural spaces and from which it is returned to the general circulation.

According to Bulson,<sup>29</sup> the infection may be borne directly by the blood stream, or travel along the outside of the vessels as they pass through the bone.

Development and Clinical Course: The development of the intracranial complications and the clinical course of the development of the latter have in most of the instances followed a fairly definite order.

Infection of the Skull. The first stage is comprised of the infection of the skull and of the development of the localized or, more commonly, diffuse form of the osteomyelitis with or without abscess formation under the scalp. In some of the cases the bone lesion is localized at the time the intracranial complication appears; in others, the osteitis has become diffuse; in very rare instances little or insignificant changes can be discerned in the bone. Luc was able to find twenty-five cases in which the intracranial lesion appeared while the osteitis was confined to the frontal bone.

Extradural Abscess. The second stage is marked by the occurrence of an external pachymeningitis. This occurs by contiguity and continuity of structure; or the transmission occurs through the vascular channels or through minute openings in the bone. The extradural infection may be at some little distance from the location of the lesion in the bone. Abscess formation is the rule. When small, the symptomatology is lost in the general clinical picture. When the abscess is sufficiently large, signs of intracranial compression become evident. The

latter may be confounded with that derived from other intracranial lesions such as brain abscess.

Should the extradural abscess communicate with the outside of the cranium through a spontaneous or operatively produced opening, and the drainage be sufficient, the physical evidences of the lesion consist in the fungous appearance of the exposed dura mater. In the absence of any drainage, or in the presence of insufficient drainage, the process almost regularly goes on to the next stage.

The third stage is a progression of the second, and according to most of the observers is produced fairly rapidly. A subdural infection occurs, and arachnoiditis and meningitis result.

Arachnoiditis; Meningitis. A serous meningitis is temporary and most commonly only precedes a more alarming condition, or less commonly disappears spontaneously and fairly rapidly. The symptomatology is exactly like that of other well established forms of meningitis; the laboratory findings differ in the important item that no organisms are demonstrable in the spinal fluid.

True arachnoiditis and meningitis in which organisms are demonstrable in the available exudate may develop directly underneath the area of osteitis or at a distance from it; the condition may be localized or may spread with rapidity over the entire brain. Luc says one variety remains localized and does not show any tendency to diffusion, and that in these cases good results may be obtained from an early and efficiently performed operation.

In the further spread of the infection beyond the three stages outlined, the process spreads to the brain and to the large venous sinuses.

Brain Abscess. Brain abscess is a common secondary complication in the fatal cases of this disease reported in the literature. The lesion is essentially similar to brain abscesses of other etiology. The abscess may be so small during the initial stage that it cannot be found on exploratory puncture, while in other cases it may occupy a large part of the lobe and may even extend behind it. The pus may be creamy or serous yellowish, green or brown, as in brain abscess of other etiology; an encapsulating membrane is sometimes present. These abscesses may be independent of any operation, and may result from the progressive extension of the infection and of the resulting lesions to the cerebral parenchyma. In some cases a previous traumatism of the cranium plays a part in the genesis of both the sinusitis and the intracranial infection.

The various stages outlined here do not always occur. In Knapp's<sup>81</sup> case in which the postmortem examination showed brain abscess as well as sinus thrombosis, there was no meningitis. This is rather unusual. A number of cases have been reported in which the brain abscess

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81. Knapp, Arnold: *Arch. Otol.* 32:181, 1903.

extended either into the arachnoid space or into ventricles. Röpke<sup>25</sup> reported two cases in which the abscess ruptured into the ventricle. These are necessarily fatal accidents. In cases of unilateral frontal sinusitis, if an abscess of the brain forms, it invariably occurs in the frontal lobe of the corresponding side. When such an abscess occurs spontaneously, it develops secondarily to extradural suppuration which is secondary to a perforation or a necrotic osteitis of the deep wall of the sinus.

Fever is the principal symptom of intracranial infection, and there are the usual secondary symptoms of loss of appetite, loss of weight and pallor. The fever is not usually very high.

Later, there are symptoms of intracranial compression. There is headache accompanied by tenderness of the region on pressure or on percussion. The headache may be lacking in exceptional cases, while in others it may be extremely severe. It is usually in the frontal region. The patient may have alimentary or bilious vomiting, and vertigo may occur. One of the most characteristic symptoms is slowness of the pulse. There may be modifications of the pupil, such as papillary stasis or atrophy of the retina. Choked disk—papillitis, neuroretinitis—are common. There are intellectual disorders, consisting of apathy and indifference. Owing to this semi-unconsciousness, many patients have incontinence of urine and feces. Delirium has been reported. It is usually mild, but in some cases there is restlessness, and the patient may attempt to rise from his bed. Unless an operation is performed within a reasonable time, coma appears and is fatal. Tonic and clonic convulsions are rare. There may be an increase in the intracranial pressure with spontaneous opening of the abscess into the ventricle or on the surface of the brain.

In other groups of symptoms, there may be clonic spasms on the side of the body opposite to the lesion in the brain. Aphasia has been noted in only a few cases. However, focal neurologic signs of sufficient clarity to indicate definitely well localized brain areas are relatively uncommon with this group of cases. The abscess may also remain latent, and hence the diagnosis is often extremely difficult. Punctures may give negative results.

Abscess of the brain is very rare in the cases of sphenoidal disease. Kramer<sup>47</sup> had one such case and said that there is only one other such case in the literature. I am indebted to him for an abstract of the notes:

A 13 year old girl, after a "cold" in the head, developed headache, nausea, vomiting, weakness, pallor and impaired vision. Pyuria and hematuria were present, and the sphenoid focus was found while the cause of the renal complication was being looked for. The patient died. Postmortem examination showed: purulent sphenoiditis, basilar meningitis and a tremendous abscess in the right frontal lobe. The pathway of infection was through a perforation in the roof of the right sphenoid, through the dura and into the right frontal lobe.

**Intracranial Venous Sinus Thrombosis.** A review of the literature makes it apparent, and only a moment's consideration will drive this home to every one, that the proportionate relationship of thrombosis or thrombophlebitis of the venous sinuses to osteomyelitis of the skull secondary to nasal accessory sinusitis, especially of the frontal and sphenoid sinuses, is exactly like that existing between thrombosis or thrombophlebitis of the lateral sinus and middle ear and mastoid disease. The similarity, therefore, extends in other particulars—pathogenesis, mechanism, clinical course, etc.

**Thrombosis of the Superior Longitudinal Sinus.** Five cases of thrombosis of the superior longitudinal sinus complicating osteomyelitis of the skull were listed by Killian in 1900. In 1909, Gerber also listed five cases, and in the same year Luc was able to collect fifteen cases. Cases were reported by Frankel,<sup>82</sup> Macewen-Miller,<sup>83</sup> Knapp,<sup>81</sup> Roth<sup>84</sup> and others. In 1914, Eckstein<sup>85</sup> collected fourteen cases of superior longitudinal sinus thrombosis complicating nasal accessory sinus disease, but an osteomyelitis was present in only six of these. Since then every year sees the reports of a few cases, usually about five or six a year. It seems, therefore, that longitudinal sinus thrombosis is not as infrequent as is commonly supposed, and that in any case in which osteomyelitis complicates the nasal accessory sinus disease, thrombosis is to be looked for; unfortunately, from the experience in the literature, the search will result successfully in a large percentage of the cases, especially as knowledge of the frequency of this complication is spread among the medical profession.

Thrombosis of the superior longitudinal sinus occurs most frequently with osteomyelitis of the frontal bone and of the skull associated with frontal and fronto-ethmoidal sinus disease. Sometimes it is found in association with other thromboses.

There are three distinct mechanisms by which this complication occurs primarily:

(1) By contact because of contiguity of structure. The superior longitudinal sinus abuts on, and is closely related to, both frontal sinuses; its anterior narrow portion reaches up to the foramen cecum.

(2) More important, the direct vascular connection between certain segments of the mucosa of the frontal sinuses and of the superior longitudinal sinus.

The venous circulation and the venous inflow into the superior longitudinal sinus is, according to Gray, as follows:

Into the superior longitudinal sinus the ethmoidal veins originating from the mucosa of the frontal sinuses and from the lateral and medial region of the nasal

82. Frankel, quoted by Luc (footnote 5).

83. Macewen-Miller, quoted by Luc (footnote 5).

84. Roth, quoted by Luc (footnote 5).

85. Eckstein: *J. Laryng., Rhin. & Otol.* 27:275, 1914.

mucosa empty. Another vein originating from the antero-lateral portion of the nasal mucosa and accompanying a branch of the anterior ethmoid artery passes through the lamina cribrosa; here it either empties into the venous plexus of the olfactory tract or it empties directly into a large vein of the orbital lobe of the brain which in its turn empties into the superior longitudinal sinus. From the frontal bone the venous blood reaches the superior longitudinal sinus through the frontal diploe which anastomose with the frontal vein. The superior longitudinal sinus receives the venous blood of all superficial veins of the hemisphere; also a few veins of the dura mater empty into it; finally it must be mentioned that in the parietal bone there is present an opening through which the superior longitudinal sinus anastomoses with the veins of the parietal region by way of the parietal emissary veins. As seen from the above, a rather extensive vascular system is connected with the superior longitudinal sinus. The phlebitis from the sinus may extend to all these veins and may give rise to many complex disease pictures.

If the anterior end of the superior longitudinal sinus is injected, numerous fine bony venules together with the mucous membrane lining certain regions of the frontal sinuses are filled with the injected substance.

In the cases of this nature which have been described in the literature, it has been pointed out that the character of such frontal sinusitis is more or less peculiar, being based on a very virulent infection, as a result of which an involvement of the superior longitudinal sinus takes place. This type of sinusitis was designated as "sinusitis exulcerans atque abscondens."

(3) By the spreading of a thrombosis or thrombophlebitis from a communicating venous sinus. There are numerous examples of this.

(4) By contact with a secondary complication, usually a discrete extradural abscess, separated and at a distance from the region of the frontal sinuses.

Thrombophlebitis of the superior longitudinal sinus gives rise to a group of characteristic secondary pathologico-anatomic changes. In most of Luc's<sup>5</sup> cases pus was found at autopsy in the superior longitudinal sinus, and in only one of his five cases the phlebitis extended to the transverse sinus. Intradural changes coexist in practically every case and usually lead to death. They have the character of circumscribed, unilateral or bilateral suppurative meningitides of the convexity of the brain. There may occur a formation of symmetrically situated inflammatory foci in the frontal lobes.

According to Killian<sup>44</sup> and other observers, the symptomatology of thrombophlebitis of the superior longitudinal sinus is quite variable. In most of the cases the disease under consideration does not give rise to severe intracranial symptoms prior to the appearance of the meningitis. In some cases meningitic symptoms are apt to appear several days before death. In some of the reported cases severe symptoms were present for only a few days, because the course of the disease was very short. Although an inflammation of the superior longitudinal sinus

gives rise to severe intracranial symptoms, the complex is not always symptomatic. In most of the cases of this type there may be found tenderness in the region of the parietal bones.

My own experience with this lesion is small. Thrombophlebitis of the superior longitudinal sinus does not appear to have been diagnosed up to the present time in cases of frontal sinusitis. Signs of this special localization are found only with difficulty. From the point of view of a focal neurologic lesion, thrombosis of the superior longitudinal sinus may be suspected when there is a tendency to, or a well established bilateral rigidity of, the extremities, confined to the lower or upper extremities alone, or existing in all four.

Luc<sup>5</sup> believes that the presence of this thrombophlebitis should be considered in cases of pyemia coinciding with an extension of the osteomyelitis to the vertex. I believe this to be a good clinical point as these venous thromboses are associated with general infections, though, curiously enough, positive blood cultures are rather uncommon with isolated thrombosis of the superior longitudinal sinus.

At the present writing, the complication is hopeless from a therapeutic point of view. Unsuccessful attempts have been made to open and drain the sinus.

**Cavernous Sinus Thrombosis.** Thrombosis of the cavernous sinus is less frequently encountered than thrombosis of the superior longitudinal sinus. The recent literature contains case reports by Faulkner,<sup>86</sup> Fotiade and Antonesco,<sup>87</sup> Guerra,<sup>88</sup> Quincy,<sup>89</sup> Todd,<sup>69</sup> Kramer<sup>47</sup> and others. The impression is given that this variety of intracranial sinus thrombophlebitis is also somewhat more frequent than is generally supposed.

Thrombosis of the cavernous sinus occurs with especial frequency in osteomyelitis of the sphenobasiocciput after sphenoid disease; such bone disease in the base of the skull is almost invariably associated with thrombosis or thrombophlebitis of the cavernous sinus. As a secondary involvement, cavernous sinus thrombosis is frequently mentioned in association with other thromboses of the intracranial venous sinuses, especially of the superior longitudinal sinus.

The mechanism for the production of the primary cavernous sinus thrombosis includes the following:

(1) By contact and contiguity with the diseased bone. The sinus lies in intimate contact with the latter.

(2) By contact with an area of meningitis at the base of the skull.

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86. Faulkner, quoted by Luc (footnote 5).

87. Fotiade and Antonesco, quoted by Luc (footnote 5).

88. Guerra, quoted by Luc (footnote 5).

89. Quincy, quoted by Luc (footnote 5).

(3) By vascular extension, especially in cases following tonsillitis or a tonsillectomy. The path lies along the venous plexus in the carotid canal.

The diagnosis of cavernous sinus thrombosis is much more easily made by its dominating symptom of proptosis of the orbital contents. Profound stupor is a characteristic manifestation. Blood cultures are usually negative.

The methods of treatment include:

(1) Ligation of the internal carotid artery.

(2) Eagleton's<sup>48</sup> operation, i. e., evisceration of the orbit and incision and drainage of the sinus.

(3) Kronlein's<sup>90</sup> operation.

Except for one or two spontaneous recoveries and a similar number of recoveries after operation recorded in the literature, this complication has uniformly resulted fatally.

Thrombosis of the other venous sinuses of the skull is much less frequently encountered than thrombosis of either the superior longitudinal or the cavernous sinuses. In the postmortem protocols, the impression is given that the other sinuses are involved secondarily and by extension from the superior longitudinal cavernous sinuses. Abscess formation has been described in the various sinuses.

In the course of the thrombophlebitis of the intracranial venous sinuses, certain stages may be differentiated:

(1) The prodromal stage. In this stage the symptoms are those of the primary lesion, fever, severe pains in the region of the forehead and headaches.

(2) Initial stage. This stage is characterized by pains in the parietal region.

(3) Stage of regional abscess (the disease is not yet generalized). The clinical symptoms of this stage vary, depending on the seat of the extracranial and intracranial abscess. In the presence of an intracranial abscess there are present generalized brain symptoms.

(4) Pyemic stage. This stage is characterized by chills, a remittent fever, pulmonary complications, swelling of the spleen, etc.

(5) The terminal stage. Meningitic symptoms develop at this stage; death occurs after from one to four days.

The terminal stage may follow directly after the initial stage. Stages 3 and 4 may occur simultaneously.

It is important to make an early diagnosis in these cases if the therapy is to be successful. A definite diagnosis can be made during the stage of the regional abscess if the abscess is characterized by

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90. Kronlein, quoted by Eagleton (footnote 48).



general cranial symptoms. Pyemic symptoms point definitely to an involvement of the sinus. The condition must be differentiated from meningitis. In cases having a fulminant course, a diagnosis is made only at the autopsy. In the great majority of the recorded cases, and in those few which I have personally seen, many intracranial lesions coexist, and it is impossible at the present time and with the present available knowledge to make any exact differentiations clinically. In every case coming to autopsy one should expect a multiplicity of intracranial complications.

#### TREATMENT

The general principles governing the treatment of osteomyelitis in general have been described on a number of previous occasions and will not be repeated here.

In the treatment of osteomyelitis, the importance of prophylaxis is greater for lesions in the skull than for those anywhere else in the body. This is especially so in the extension type of case following nasal accessory sinus disease. Prophylaxis should include these objectives: (*a*) appropriate measures for the possible prevention of any preceding condition to which the osteomyelitis of the skull is commonly secondary; (*b*) the proper immediate care of all scalp wounds, especially those extending into the bone; (*c*) the efficient treatment of all nasal accessory sinus disease, and (*d*) the improvement in the general condition of the patient. When any of these precautions include operative manipulations anywhere near any part of the cranial diploe, extreme care should be exercised not to involve this very vulnerable tissue in the infective process.

#### CLASSIFICATION FOR TREATMENT

In osteomyelitis of the skull the cases can be divided into the following groups, as far as the necessary treatment is concerned: (1) cases with the clinical signs of a general infection; (2) cases with little or no signs of a general infection, but with various grades of a local restricted or circumscribed lesion; (3) cases of diffuse spreading osteomyelitis of the skull and (4) cases with intracranial complications.

*Cases with General Infection.*—Highly fulminant forms of general infection (sepsis, septicemia, etc.) are usually of such a high order of severity as to make futile any therapeutic endeavor. They are also commonly associated with a variety and diversity of intracranial complications (meningitis, sinus thrombosis of the longitudinal or cavernous sinuses etc.), each one of which by itself is, practically speaking, beyond one's efforts to cure except for a few fortunate cases reported in the literature.

In less highly fulminant cases it frequently happens that attention to the local bone lesion results in an amelioration of the clinical picture and

a subsidence of any accompanying general infection. The periods of remission which are commonly seen are most frequently related to revisions of the local condition. However, it is only too common also for recrudescences to follow subsequently with an eventful fatality.

*Cases with Local Circumscribed Lesions.*—Cases of this type lend themselves to efficient treatment only when they are in the vault and the neighboring parts of the skull, including the mastoid, and adjacent parts of the occipital bone posterior to the foramen magnum, the accessible parts of the orbital boundaries including the ethmoid, the lacrimal bone, the nasal process of the superior maxilla and the part of the sphenoid that presents in the roof of the nasopharynx.

Efficient treatment of this class of lesion requires the thorough removal of all infected bone, preferably by removal en masse with the line of resection in healthy tissue at an appreciable distance from the infected bone. The dura should not be opened purposely, and the accidental opening of it is a most deplorable accident. The venous sinuses also should not be tampered with unless there is clinical and operative evidence of thrombosis; then, whenever possible a technic similar to that in use for similar conditions in the lateral sinus complicating mastoid disease should be employed.

At any other area away from the vault of the skull efficient complete removal of the disease is commonly impossible; this applies with special force to disease in the ethmoid and in the sphenoid; incomplete operations should be fortified by wide and free drainage, but it must be freely admitted that in these areas the prime indication of complete removal of the disease is never met, and recrudescences are common and frequently of ominous character.

The base of the skull, especially the area comprised in the adjoining parts of the posterior part of the body of the sphenoid, the petrous pyramid and the basiocciput are beyond reach by surgical means; the parts are inaccessible. The danger of uncontrollable hemorrhage is very great; the danger of injury to important nerves is equally large, and the chances of a secondary intracranial infection is almost 100 per cent.

No matter where the disease exists, if it once involves the diploic tissue and veins, a condition is present in which the progression of the lesion seems to be independent of all ordinary therapeutic measures. The lesion is a progressive, self limited one—all too frequently limited by death—in which there is a continuous, contiguous molecular advance of the process, or a diffusion of the infection by repeated series of thrombo-embolisms by which additional areas, separated from the main seat of the disease by slight intervals, are attacked and involved. It is for this reason that it is imperative to remove by operation wherever possible every bit of tissue carrying any infection; the resection should

be very wide, and it is much better to err on the more radical side and remove more, than to remove less and subject the patient to the danger of recurrence. Anything less than complete removal invites disaster. Clinical experience bears this out; the possibility for complete cure is limited to cases in which the diseased area is present only in the accessible regions of the vault of the skull; at the base of the skull in the spheno-petro-basiocciput the mortality is, practically speaking, 100 per cent because removal of the basic infection is not possible.

*Cases of Diffuse Spreading Osteomyelitis of the Skull.*—Diffuse spreading osteomyelitis of the skull is the corollary of the remarks made in the preceding paragraph. Its presence is due to insufficient checking of the lesion by operative means, and its cure depends on the capability and possibility for complete removal of the infected area.

I am under the impression—and I am sorry that I have not up to the present had the opportunity of carrying out the method—that in these cases the maggot treatment of osteomyelitis might be valuable. I mention it here for what it is worth and hope that the method will soon have an opportunity to prove itself in these otherwise difficult cases.

*Cases with Intracranial Complications.*—The treatment of the various complications that have been outlined in this communication depends on the various individual or associated lesions encountered, which are either beyond reach at the present moment—as in some of the venous sinus thrombosis cases—or are reached according to well established principles. It is beyond the scope of this paper to go into the latter at any length, except for the therapeutic indications that accompany the development of a meningitis.

In any case of osteomyelitis of the skull, one should constantly be on guard for the occurrence of meningitis. Continued headache, vomiting and slow pulse should be accepted as prodromal signs of some impending intracranial complication until the assumption is definitely disproved. Rigidity of the neck, a Kernig sign, restlessness and hyperexcitability should intensify one's suspicions. The association of these subjective and objective symptoms should indicate the extreme urgency of the condition. A spinal tap should be done immediately; two possibilities are present:

1. Spinal fluid is obtained in increasing amounts which show on microscopic examination an abnormal number of pus cells, but the absence of any organisms. This is the stage of meningeal irritation and indicates that an inflammatory lesion is in close contiguity with the meningeal membranes.

In the absence of signs pointing to the presence of other intracranial lesions—venous sinus thrombosis, brain abscess, etc.—it should be assumed that the abnormality of the spinal fluid represents an irritation

phenomenon, the source of the irritation being in the infected bone tissue of the skull. If subsidence and disappearance of the irritation phenomena are not prompt, and no signs are present pointing to the presence of other associated intracranial lesions, the indication is present to explore the bone on which operation has not been done or to revise that which has already been operated on, to remove from it all diseased tissue and to drain adequately any associated extradural collections of pus.

2. Spinal fluid is obtained freely under increased pressure, which shows on microscopic examination a preponderating majority of pus cells and the presence of few or many organisms which are viable and are easily culturable. This is the stage of established inflammation of the meninges—frank meningitis. Blood cultivations are frequently positive.

Therapy of any kind is usually ineffective in the cases of established meningitis for the following reasons: (*a*) the practical impossibility of controlling this type of meningitis itself; (*b*) the presence of other intracranial lesions—venous sinus thrombosis especially—which are for practical purposes beyond cure at the present time, and (*c*) the presence of an established and progressive general infection as shown by a demonstrable bacteremia.

#### MORTALITY

A considerable number of deaths have followed osteomyelitis of the skull. The fatal issues have resulted from the following circumstances: (1) the intensity of the local lesion, its persistence and the tremendous facility and ready opportunity for the spread of the disease; (2) the readiness with which exacerbations of infection occur in the primary lesion in the extension group of cases, leading to similar exacerbations in, or to the renewed spread of, the osteomyelitis in the cranium; (3) the extraordinary difficulty in adequately removing the disease; (4) the extreme frequency of intracranial complications which furnish the largest proportion of the fatal cases, and (5) the occurrence of general infection (bacteremia, sepsis, septicemia, etc.).

Difficulty in correctly appraising the numbers of patients "cured" and "not cured" and the fatal cases is mostly due to the fact that the condition is marked by many remissions, and the patients naturally drift many times from hospital to hospital and from clinic to clinic. An idea of the correct situation as regards the mortality of osteomyelitis of the skull can be found in the attached statistics:

GERBER.<sup>26</sup>—Total number of cases, twenty-nine; no cures; twenty cases terminated fatally.

McKENZIE.<sup>27</sup>—Total number of cases, forty-one; twenty-one cases of spontaneous osteomyelitis after nasal accessory sinus disease with fourteen deaths; twenty cases after operation for nasal accessory sinus disease with twenty deaths.

tion because of abscess of the lung, cancer of the ovary and sepsis of the joint, respectively. Of the group, two were not operated on but are included because of a potential surgical condition. The cases in this group are presented in table 1. In seventeen instances there was a preceding history of anorexia, undernutrition or intermittent vomiting of several weeks' duration. The five patients operated on for acute appendicitis were previously well. They all had ruptured appendixes. Postoperative drainage was profuse in each instance. Eight patients had observed edema of the extremities before operation. The postoperative edema was noted as a rule about seven days after surgical intervention. It was seen as early as two days after operation and as late as fifteen days after. Once it was noted at operation. Edema was present in every case and varied in degree only. Those showing moderate edema usually manifested it in the ankles, legs or genitalia. In those cases with the most marked edema there was an accumulation of fluid in all the dependent portions of the body, the peritoneal cavity, the walls of the digestive tract and mesentery and the lungs. In nine patients only slight pitting edema of the legs and ankles or of the genitals was noted. The remainder showed edema up to the point of anasarca. Five had definite edema of the lungs, and in two of these oxygen therapy was necessary. Edema of the stomach or intestinal wall was known to have been present in three cases, and because of postoperative vomiting or gastric stasis as indicated by lavage, it was thought that eight patients gastro-enterostomized patients had edema of the stomach, of the gastro-enterostomy stoma or of the intestine, with resulting partial obstruction. Four patients, at least, had diarrhea as a result of edema of the intestinal wall. One patient died directly as a result of the edema of the intestinal wall with resultant partial obstruction. Two other patients were temporarily in a critical condition as a result of the generalized edema and would undoubtedly have died if diuresis had not been obtained.

Blood analyses, usually made at the time edema was noted, included determinations of serum protein, serum albumin, nonprotein nitrogen and chlorides. Unfortunately, all four determinations were not made in every instance, but for the most part the chemical studies were reasonably complete. In nearly every instance there was no evidence either before or after operation of any abnormality of renal function. The exceptions will be specifically mentioned. The only urinary finding of importance was a rather striking elevation of the specific gravity. The surgical procedures included gastro-enterostomy, with or without partial gastric resection, appendectomy with drainage, cholecystoduodenostomy, surgical drainage of sepsis and exploratory laparotomy. Postoperative care included routine surgical measures, including the administration of fluids by various routes. Fluids by mouth were

TABLE 1.—*Data on Patients with Demonstrable Edema Following Surgical Procedures*

Case	Age	Diagnosis	Operation	Serum	Serum Nonprotein			Edema
				Albumin, Gm.	Protein, Gm.	Nitrogen, Mg.	Chlorides, Mg.	
1	45	Obstructing ulcer	Posterior gastro-enterostomy	...	6.5 5.8	80 47	603 590	+
2	65	Obstructing ulcer	Posterior gastro-enterostomy	3.0	5.5 27	20	585	+
3	52	Cancer of stomach	Exploratory	2.4	5.1	41	616	+
4	44	Cancer of stomach	Exploratory	2.5 3.1	4.7 5.2	41 26	632 578	+
5	52	Cancer of pancreas	Cholecystoduodenostomy	2.2 4.2	4.4 5.8	23 32	517 462 509	+++
6	63	Cancer of pancreas	Exploratory	...	4.5	125	892	+
7	45	Gastric ulcer	Posterior gastro-enterostomy	...	5.3 5.0	37 32	661 695 622	+
8	55	Cancer of stomach	Resection	...	4.7 5.6 4.6	25 23	(585)	++
9*	47	Gastric ulcer	Resection	...	4.4 4.4	..	488 574	++
10	38	Cancer of stomach	Resection	1.9 3.6 2.4	3.7 5.6 4.4	45 37 40	665 524 609	+++
11*	57	Cancer of stomach	Resection	...	6.2 4.4 6.5	35 25 27	512 622 570	++++
12	62	Gastric ulcer	Posterior gastro-enterostomy	...	4.5	50	658	++++
13	60	Cancer of stomach	Posterior gastro-enterostomy	...	7.0 5.5	40	538 606	+
14	60	Cancer of stomach	Posterior gastro-enterostomy	3.3	7.4 5.7 7.2	43 30 110	506 579 468	+
15	43	Perforated appendix	Drainage	2.9 4.8	5.2 6.8	39 30	555	++
16	13	Perforated appendix	Drainage	3.0 3.5	4.9 5.6	23 22	561 555	+
17	28	Perforated appendix	Drainage	...	5.5	30	...	+
18	14	Perforated appendix	Drainage	3.5	4.4	41	...	++
19	15	Perforated appendix	Drainage	...	...	..	541	++
20	60	Fecal fistula	Closure	3.9	5.5 7.0	36	506	+
21	39	Lung abscess	Drainage	1.6 3.0	5.6 6.4	32 22	588 570	++
22*	52	Cancer of ovary	Resection	...	4.7 4.1 5.6	..	(495) 537	++
23	50	Cancer of intestine ?	Appendectomy; diarrhea	2.9 2.6	5.5 3.1	55 20	692 698	+++
24	48	Cancer of intestine ?	Diarrhea	1.4 2.1	4.0 3.1	41 28	547 515	+++
25	40	Joint sepsis	Drainage; transfusion; reaction	3.3 2.6 4.2 4.0	5.5 4.4 7.3 6.5	195 260 91 33	562 628 564 564	++
26	45	Duodenal ulcer	Hemorrhage	...	4.4 6.2	22	595	++

\* The data on these patients who were being cared for at the New England Deaconess Hospital were made available through the courtesy of Dr. Leland S. McKittrick.

usually restricted. Rectal taps were either of water or of physiologic (0.9 per cent) solution of sodium chloride combined with 5 per cent dextrose. Hypodermoclysis consisted in the administration of 2.5 or 5 per cent dextrose in physiologic solution of sodium chloride. Fluids for intravenous administration were, with rare exception, physiologic solutions of sodium chloride containing 5 or 10 per cent dextrose.

It will be seen from table 1 that with few exceptions the degree of edema varied inversely with the serum protein content and somewhat less consistently with the serum albumin. The level of the nonprotein nitrogen bore no relation to the presence of edema, and for the most part the figures obtained were within normal limits, or only slightly above normal. Three notable exceptions occurred in cases 1, 6 and 25. Values for blood chloride interestingly enough were normal or well above normal in over two thirds of the cases, probably because of the administration of large amounts of sodium chloride. The specific gravity of the urine was high in nearly all the cases at or near the time that edema was noted. It ranged from 1.015 to 1.040, with the majority of the figures between 1.025 and 1.035.

With the foregoing facts in mind, it will be of value to consider several of the cases in greater detail. Protocols of some of the more striking cases follow.

#### REPORT OF CASES

CASE 12.—A man, aged 62, had a condition diagnosed obstructing pyloric ulcer. For fifteen years he had had intermittent ulcer. Successful intensive medical treatment had been given twenty-one months previous to admission. Generalized edema at this time was relieved while the patient was receiving ulcer therapy. There had been intermittent vomiting for three months, with marked anorexia and some loss of weight.

Physical examination on admission gave essentially negative results, except for edema of the legs, genitals and abdominal wall. Studies of renal, hepatic and cardiac function all were negative. The preoperative serum protein was 5.7 Gm. per hundred cubic centimeters; nonprotein nitrogen, 43 mg., and chlorides, 599 mg.

Edema disappeared with rest in bed and a fair intake of milk and cream.

Posterior gastro-enterostomy was performed for a partially occluding pyloric ulcer. During the first seven days after operation there was obvious gastric stasis, which was relieved by vomiting or gastric lavage. The urinary output was moderate in amount, averaging from 800 to 900 cc. per day, and the specific gravity was high throughout (from 1.030 to 1.034). On the seventh day after operation edema developed rapidly in the feet, thighs and scrotum, and increased in degree after the next week. Digitalization produced no diuresis. The urine was normal, except for the high specific gravity. The vomiting, which had diminished in severity, again became troublesome, and, in addition, on the tenth day a very watery diarrhea developed. Pulmonary edema was evident on the thirteenth day, and the patient died on the following day.

Autopsy showed the local operative findings, anthracosis and anasarca. The walls of the jejunum and ileum were very edematous, and the cause for the mal-functioning gastro-enterostomy was obviously edema of the intestinal wall.

A summary of the fluid intake during the first seven days after operation is important. The patient received the following fluids:

Intravenous administration.	3,900 cc.	Total fluid intake.....	29,500 cc.
Subpectoral .....	10,500 cc.	Vomitur .....	2,000 cc.
Oral .....	5,400 cc.		7) 27,500 cc.
Rectal .....	9,700 cc.		

Average daily fluid intake. 3,928 cc.

The intravenous and subpectoral solutions were made up of dextrose in physiologic solution of sodium chloride (0.9 per cent) and contained a total of 130 Gm. of sodium chloride. The average daily fluid intake was nearly 4 liters and contained at least 18 Gm. of sodium chloride.

On the seventh day after operation the chemical examination of the blood showed: serum protein, 4.5 Gm. per hundred cubic centimeters; nonprotein nitrogen, 50 mg., and chlorides, 658 mg.

CASE 1.—A man, aged 48, had a condition diagnosed obstructing duodenal ulcer. He presented a fairly suggestive history of ulcer for many years. For fifteen months he had had distress in the upper abdominal region relieved by vomiting. The frequency and degree of vomiting increased gradually until admission, with consequent weakness and loss of 30 pounds (13.6 Kg.) in weight. The remainder of the history was irrelevant.

Physical examination revealed an emaciated man. The heart was normal. The abdomen was distended, apparently due to a dilated stomach. There was visible peristalsis. Otherwise the results of the physical examination were essentially negative.

Laboratory examination revealed the following data: urine, normal; red blood cells, 3,090,000 per cubic millimeter; hemoglobin, 60 per cent; serum protein, 6.5 Gm. per hundred cubic centimeters; nonprotein nitrogen, 80 mg.; chlorides, 608 mg.; serum protein, 5.8 Gm.; nonprotein nitrogen, 47 mg., and chlorides, 590 mg.

For four days before operation the patient received a daily intravenous injection of about 1,250 cc. of 10 per cent dextrose in distilled water, and, in addition, an equal amount by oral or rectal administration. Although no sodium chloride was given intravenously, alkaline powders were given for two days before the operation with at least a daily intake of 22 Gm. of sodium bicarbonate. It is to be noted that preoperatively the serum protein had dropped from 6.5 Gm. per hundred cubic centimeters to 5.8 Gm.

On exploration, an obstructing healed duodenal ulcer was found, and a routine posterior gastro-enterostomy was performed. The following operative note was made: "There was much more than the usual amount of fluid in the abdomen. There was very marked edema of the stomach and the transverse mesocolon."

For the first three days after operation the gastro-enterostomy obviously did not function properly, as was evidenced by the amount of vomitus and gastric lavage (1,470 cc.). On the fourth day marked improvement was noticeable, and convalescence was thereafter uneventful. It is of interest to note that no further clyses or intravenous injections were administered after the third day.

A summary of the fluid intake during the first three days after operation was as follows:

Intravenous administration..	1,750 cc.	Total fluid intake.....	9,350 cc.
Subpectoral .....	5,800 cc.	Vomitur .....	1,470 cc.
Oral .....	1,800 cc.		3) 7,880 cc.

Average daily fluid intake. 2,627 cc.

The total amount of sodium chloride given by intravenous injection and by hypodermoclysis was 68 Gm., or an average daily amount of 22.6 Gm.



CASE 10.—A woman, aged 38, had a condition diagnosed cancer of the stomach. Her history was essentially unimportant until seven weeks before admission, at which time she began to have vague pain in the upper abdominal region without relation to meals. Vomiting without hematemesis accompanied the abdominal distress and, subsequently, marked constipation. She had lost about 60 pounds (27.2 Kg.) during the eight months before admission.

Physical examination showed an emaciated woman with a palpable mass the size of a hen's egg in the region of the stomach. There was slight pitting edema of the extremities. Roentgenograms of the gastro-intestinal tract showed an obstructive pyloric lesion with complete retention of the motor meal.

Exploration revealed a nodular growth involving the antrum, with regional glandular involvement. A large resection and a posterior gastrojejunostomy were performed. During the six days after operation the patient was able to take only small amounts of fluid by mouth but received by various routes a total of 17,000 cc., or a daily average of 2,840 cc. The daily average salt intake was approximately 19 Gm.

On the fifth day after operation there were signs at the bases of the lungs, and twenty-four hours later cyanosis was extreme enough to necessitate an oxygen tent. The signs were not those of partial collapse or of pneumonia, but were more consistent with pulmonary edema. Three days later there was massive edema of the hands, feet, legs and flanks. Three transfusions of 500, 600 and 600 cc. were performed in the next five days, during which period there was marked abdominal distention and watery diarrhea. At this point severe stomatitis developed, similar to that noted in case 15. Following the third transfusion the edema diminished slightly, but there was evidence of increasing pulmonary edema and gastric retention, as demonstrated by gastric lavage yielding 780 cc. The patient died on the fifteenth day after operation.

Autopsy showed in addition to the operative findings and a walled-off abscess between the stomach, liver, colon and anterior abdominal wall, evidences of edema of the legs, vulva, pleural cavity and lungs. There was about 1,000 cc. of thin yellow fluid in the peritoneal cavity, which may have been associated with nutritional edema or with the inflammatory process in the abdominal cavity or with both. Microscopic examination of the lungs showed many of the alveoli filled with serum and slight edema of the submucosa in the intestine.

Chemical examination of the blood revealed the following: Eight days after operation, the serum protein was 3.7 Gm. per hundred cubic centimeters; serum albumin, 1.9 Gm.; nonprotein nitrogen, 45 mg., and chlorides, 665 mg. A transfusion of 500 cc. of blood was given.

Ten days after operation the serum protein was 4.2 Gm. per hundred cubic centimeters; nonprotein nitrogen, 36 mg., and chlorides, 621 mg. A transfusion of 600 cc. of blood was given.

Twelve days after operation the serum protein was 4.4 Gm. per hundred cubic centimeters; nonprotein nitrogen, 37 mg., and chlorides, 602 mg.

A summary of the fluid intake during the first six days after operation is as follows:

(Hypodermoclysis, 1,000 cc. one day before operation)			
Intravenous administration.	3,900 cc.	Total fluid intake.....	17,080 cc.
Subpectoral .....	10,500 cc.	Daily average .....	2,846 cc.
Oral .....	5,400 cc.		
Rectal .....	2,880 cc.		

The average daily intake of sodium chloride was 22.9 Gm.

CASE 11.—The patient, aged 57, had a condition diagnosed cancer of the stomach. The past history was irrelevant. For two months the patient had sui-

ferred from epigastric distress, nausea, and finally obstructive vomiting. Physical examination revealed an emaciated patient with an obviously enlarged stomach and a palpable mass in the region of the pylorus. Roentgenograms showed a grossly obstructive lesion at the lower end of the stomach. Operation was decided on, and at exploration a large obstructing lesion was found; a very wide resection was performed together with an anastomosis between the jejunum and the remainder of the stomach. The wall of the stomach was very edematous.

On the day preceding the operation the patient received an intravenous injection of 750 cc. of dextrose in physiologic solution of sodium chloride, and on the day of operation 4,000 cc. by clysis and by vein. The serum protein on this day was 6.2 Gm. per hundred cubic centimeters. Four days later the serum protein had dropped to 5.2 Gm., and the blood chlorides had risen to 611 mg. Three days later, or six days after the operation, the serum had reached a level of 4.4 Gm., and the blood chlorides were at the level of 578 mg. During this seven day period the average daily fluid intake was 3,187 cc., 2,070 cc. of which was introduced by vein or by clysis, with a salt intake of 18.6 Gm. a day. Edema of the feet and left arm was noted on the second day after operation, and by the fifth day anasarca was present, involving even the cheeks and lips. From the third day after operation the fluid intake was reduced steadily, until on the seventh day after operation it amounted to only 860 cc. With the marked reduction in the administration of fluid and salt, diuresis was prompt, and the demonstrable edema, which had reached its peak coincidentally with the greatest drop in serum protein, receded rapidly. It had completely disappeared by the tenth day, at which time the serum protein was normal. From the third day, however, vomiting was a constant feature, and this may have been due to edema of the stomach and gastro-enterostomy. The vomiting undoubtedly was a contributory factor in the lowering of the blood chlorides to 479 mg. per hundred cubic centimeters.

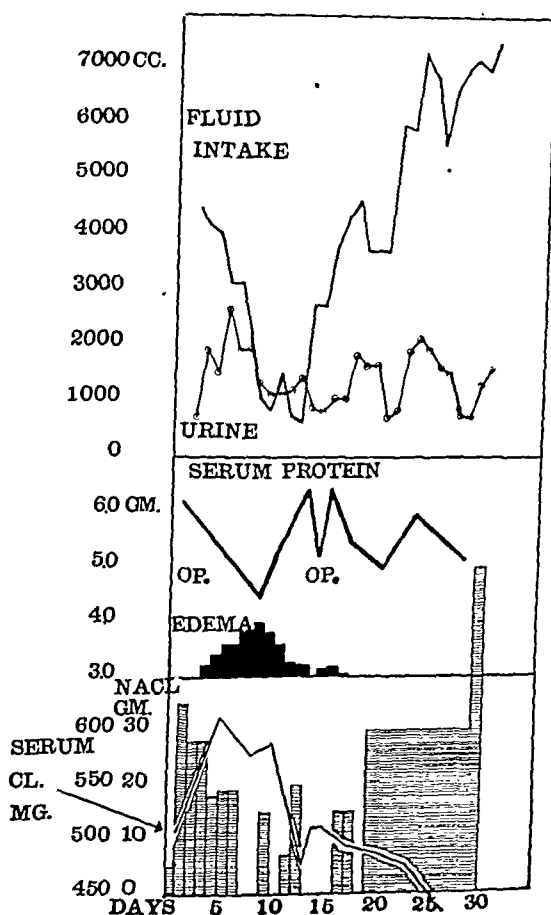
Because of the persistent vomiting, a jejunostomy was resorted to, and for three days moderate edema again returned. As soon as possible after the second operation a generous amount of protein and salt was given by jejunostomy, and this plus transfusion resulted in a temporary rise in serum protein and blood chlorides. Edema did not recur, but complications around the enterostomy resulted in final complete obstruction and eventual death. During the latter period the serum protein and blood chlorides dropped despite an adequate protein and salt intake via the jejunostomy.

A graphic representation of the findings in this case is given in the chart. The time relations between the high fluid and salt intake, the lowering of the serum protein and the development of edema are readily noted.

CASE 15.—A woman, aged 43, had a condition diagnosed perforated appendix. The history was essentially unimportant until three days before admission. At this time there was sudden onset of pain in the right lower quadrant with nausea, vomiting, fever and chill. The patient was brought to the hospital where a diagnosis of acute appendicitis was made. Operation was immediately performed. A gangrenous appendix was found; it was removed, and drainage was instituted.

Drainage was profuse for several days. During the first six days after the operation the patient received clyses and intravenous injections of 2.5 per cent dextrose in physiologic solution of sodium chloride aggregating 12,700 cc., or an average daily amount of 2,116 cc. The sodium chloride intake by these injections amounted to 19 Gm. daily. At the end of the sixth day edema of the extremities was noted, and, in spite of discontinuing intravenous injections and hypodermoclysis, it increased rapidly so that on the following day there was anasarca. Cyanosis was so marked from pulmonary edema that an oxygen tent was necessary. Digitalis was given, a common procedure, but presumably was of no value. As

emergency measures, 50 per cent dextrose was given intravenously and 2 cc. of salyrgan. Diuresis was prompt, and in two days there was marked improvement. Five days after the appearance of massive edema the patient received a transfusion of 250 cc. of blood and three days later a second one of a similar amount. Following the two transfusions, diuresis continued for almost a week. From that point convalescence was uneventful. It is of interest to note that severe stomatitis occurred two weeks after operation.



Effect of administration of fluid and salt in the production of postoperative nutritional edema. Observations were made on a patient with cancer of the stomach (case 11). Edema was observed two days following a resection and a gastro-enterostomy, and reached its peak on the ninth day.

A summary of the fluids given for six days after operation and of the laboratory findings is as follows:

Intravenous administration..	6,200 cc.	Total fluid intake.....	12,700 cc.
Clysis .....	6,500 cc.	Average daily fluid intake..	2,116 cc.
Oral .....	Small amount		

The total amount of sodium chloride given by clysis and intravenous injection was 114 Gm., or an average daily intake of 19 Gm.

Six days after operation the serum protein was 5.3 Gm. per hundred cubic centimeters; serum albumin, 3.4 Gm., and nonprotein nitrogen, 39 mg.

Salyrgan, 2 cc., and 50 per cent dextrose were administered intravenously.

Nine days after operation the serum protein was 5.3 Gm. per hundred cubic centimeters; serum albumin, 2.9 Gm., and nonprotein nitrogen, 27 mg.

Two blood transfusions were given of 250 cc. each.

Eighteen days after operation the serum protein was 6.9 Gm. per hundred cubic centimeters; serum albumin, 4.8 Gm., and nonprotein nitrogen, 30 mg.

CASE 17.—A man, aged 28, had a condition diagnosed perforated appendix. The history was unimportant except for a single attack of sharp pain in the right lower quadrant three years previous to admission. Eight days prior to admission the patient had intermittent epigastric pain, associated with nausea and vomiting. Later the pain shifted to the right lower quadrant, and there was further vomiting. He entered the hospital because of the continuation of his symptoms, and a diagnosis of acute appendicitis was made. Operation was performed at once, and an appendical abscess was found which was drained. During the following six days drainage was profuse. During this period the patient received an average of 3,870 cc. daily by intravenous, subpectoral and oral routes. The average daily sodium chloride intake was about 23 Gm. On the third day in particular the fluid intake, by error, was 7,800 cc., with a salt content of almost 62 Gm. The patient showed probable pulmonary edema at the end of the second day, vomited off and on for the next six days, and had pitting edema of the feet at the end of the eighth day. The serum protein at this time was 5.5 Gm. per hundred cubic centimeters and probably had been lower a few days previous. At this point he was able to take a reasonable amount of protein by mouth and convalescence was thereafter uneventful.

A summary of the fluid intake for six days after operation is as follows:

Intravenous administration..	9,865 cc.	Total fluid intake.....	24,060 cc.
Subpectoral .....	5,200 cc.	Vomit .....	1,840 cc.
Oral .....	8,995 cc.		6)23,220 cc.
Average daily fluid intake.			3,870 cc.

The average daily intake of sodium chloride was 22.6 Gm.

CASE 26.—A woman, aged 45, had a condition diagnosed bleeding duodenal ulcer. Although no operation was performed on this patient, the case is presented because an operation might well have been considered. Her past history was irrelevant. The present illness was of one month's duration and consisted only of indefinite epigastric distress until three days before admission, at which time she passed two large tarry stools and one containing red blood. The following day she vomited a pint of blood, liquid, and passed another tarry stool. The day of admission she vomited three times, each time about a pint and a half of black and reddish vomitus.

Physical examination showed an obese pale woman in no distress. The pulse was 104 and the blood pressure was 150 systolic and 82 diastolic. There was slight edema of the left lower leg.

On admission, her red blood count was 1,550,000 per cubic millimeter with a hemoglobin of 45 per cent. She vomited more blood the following day, and on the seventh day of her acute illness her count had dropped to 1,030,000 and the hemoglobin to 30 per cent. She was given a blood transfusion, but a further hemorrhage occurred, and on the seventeenth day her red count was 950,000 per cubic millimeter with a hemoglobin of from 25 to 30 per cent. On the next day she was given another transfusion and had a severe reaction, characterized by a rise in temperature and a chill. The following day there were signs of pulmonary edema at the base of the right lung, and the next day there was edema of the face, eyelids, hands, legs and trunk. There were signs of pleural effusion on the right side.

During the three weeks preceding the development of edema, the patient had received relatively little fluid by mouth. For a week preceding the development of edema, sodium bicarbonate had been administered in combination with bismuth or calcium carbonate. The amount of alkali administered in combination had been sufficient on the twentieth day to produce a moderate but real alkalosis. Sodium had also been administered in the form of sodium chloride in rectal taps. The total amount cannot be determined.

Chemical examination of the blood revealed the following:

Twenty days after the onset of the illness the serum protein was 4.4 Gm. per hundred cubic centimeters; nonprotein nitrogen, 19 mg.; chlorides, 508 mg., and the carbon dioxide-combining power, 78.8 per cent by volume.

Twenty-seven days after the onset the serum protein was 5.4 Gm. per hundred cubic centimeters and the carbon dioxide-combining power, 59.2 per cent by volume.

Thirty-four days after the onset the serum protein was 6.2 Gm. per hundred cubic centimeters.

From the twentieth day after the onset of her illness, possibly because of a high protein diet given in frequent small feedings, there was gradual diminution in the edema and a good diuresis. There was no further bleeding, and with the subsidence of edema the patient lost 10 pounds (4.5 Kg.) in weight in spite of a gradually increasing food intake. Alkali was discontinued as soon as it was realized that a mild alkalosis existed. In one week after the height of the edema the serum protein was 5.4 Gm. per hundred cubic centimeters, and the carbon dioxide-combining power was 59.2 per cent by volume. One week later the serum protein had risen to 6.2 Gm. Shortly thereafter the patient was discharged, free from edema, and with a red count returning steadily to normal. Roentgenograms of the gastro-intestinal tract showed a duodenal ulcer. The relation of this case to abdominal surgery will be considered later.

CASE 25.—The patient, aged 49, had a condition diagnosed sepsis of the joint. Drainage and transfusion had been employed. The history was essentially unimportant except for the present illness. For four years, following a previous operation on the hip, the right hip joint had had continuous drainage of purulent material with resulting local pain and disability. Physical examination showed little beyond the local condition except some general loss of weight. There was no evidence of tuberculosis. Routine laboratory studies were negative.

On September 17, a posterior drainage of the right hip joint was performed. On October 10, an arthrodesis of the hip was done followed by continuous drainage. Two weeks later, because of an anemia of 2,220,000, and in order to hasten convalescence, a transfusion of 600 cc. of whole blood was given. The patient had an immediate and severe reaction followed by fever, chills and vomiting. The next day the vomiting persisted, and the patient was slightly jaundiced. The urine, which was scant and very concentrated, retained a trace of albumin and numerous red cells. For the next ten days the patient had marked oliguria, anorexia and nausea. On November 4, he was vomiting and was extremely dehydrated and somewhat irrational. The urine still continued to show a trace of albumin, and the nonprotein nitrogen was 200 mg. per hundred cubic centimeters. There was edema of the affected leg, which was at first thought to be due to pressure of the cast. Blood studies the following day showed a serum protein of 5.5 Gm. per hundred cubic centimeters, a nonprotein nitrogen of 195 mg., and blood chlorides of 562 mg. It was felt that the condition was essentially one of extreme dehydration following a reaction to the transfusion with a partial renal shut-down, and fluids were given rather freely in spite of the danger of producing edema. Diuresis was promoted by the use of a 50 per cent solution of dextrose in distilled water and by the use of salyrgan. For the next eight days the average daily fluid intake

was 2,800 cubic centimeters, with a total of 36 Gm. of sodium chloride given in two intravenous injections. Edema of the face and leg was obvious on the first day of intensive therapy and rapidly increased, until on the fourth day generalized edema with ascites and pulmonary edema was present. The latter was associated with cyanosis and orthopnea. During the period of eight days the serum protein dropped to 4.3 Gm. and then, as diuresis became established, rose to 6 Gm. The nonprotein nitrogen rose to 211 mg. and did not fall appreciably until ten days after intensive treatment started. The patient vomited persistently and was very irrational for about ten days, and during the first three days was bothered by a severe watery diarrhea. After about the seventh day diuresis was striking, and from then on the edema rapidly subsided. The general condition improved gradually, however, and the nitrogen retention persisted for three weeks after active treatment started. With a return of the blood to normal the urine cleared completely, and convalescence was thereafter uneventful. A tabulation of the important findings follows:

	Intravenous Adminis- tration, Cc.	Total Fluid, Cc.	Serum Protein, Gm.	Serum Albumin	Non- protein Nitrogen	Edema
November 5.....	2,100	3,300	5.5	3.2	195	+
November 6.....	1,200	2,500	4.3	2.6	260	++
November 7.....	1,900	2,900	5.5	2.6	205	+++
November 8.....	250*	2,200	...	...	...	++++
November 12.....	Diuresis excellent from November 9		6.0	3.4	205	+
November 16.....	Liberal fluid intake by mouth		7.3	4.2	91	?
November 23.....	.....	.....	6.5	4.0	33	0

\* 25 per cent dextrose.

Salyrgan was given on November 5 and November 6.

In table 2 are given brief data on eight other cases. The patients observed in this group presented conditions similar to those presented in the previous one. In every case but one (no. 32) there was an underlying condition which laid the foundation for marked undernutrition. Case 32 corresponded to the cases of acute gangrenous appendicitis outlined in the preceding group. In each instance there was a marked lowering of serum protein to the critical level. Demonstrable edema was not observed, however, either because the figures for serum albumin did not drop to the critical level, or because fluids and salt were not pushed to sufficiently high levels to produce a noticeable accumulation of fluids. It is obvious, however, that these were all borderline cases in which slight excesses in the administration of fluid and salt would have produced real difficulties.

#### COMMENT

A consideration of the foregoing data indicates that nutritional or inanition edema may readily occur as a complication of many surgical conditions. The majority of the patients observed were undernourished prior to operation because of malignancy, pyloric obstruction and similar conditions. Actual vomiting as well as loss of appetite contributed to such a situation. In one instance (case 12) edema had

been noted prior to operation. Following a surgical procedure in every instance the process of undernutrition was continued for several days by the very nature of the operation performed. In addition, the situation was further aggravated by the administration of relatively large amounts of fluids and salt. Table 3 indicates the amounts of fluid administered during the first few days after operation. It will be noted that the actual amount of fluid given daily in the cases of gastric dis-

TABLE 2.—*Data on Patients with No Demonstrable Edema, but with a Lowered Serum Protein, Following Surgical Procedures*

Case	Age	Diagnosis	Operation	Serum Albumin, Gm.	Serum Protein, Gm.	Nonprotein Nitrogen, Mg.	Chlorides, Mg.
27	50	Obstructing ulcer	Posterior gastro-enterostomy	3.5	7.0	92	441
				4.5	5.6	173	569
28	42	Duodenal ulcer	Posterior gastro-enterostomy	...	7.3	..	585
				3.4	5.5	25	585
				4.1	6.6	37	555
				3.8	6.1	25	...
29	45	Gastric ulcer	Resection	5.5	6.8	40	585
				4.2	5.3	26	625
30	63	Ulcerative colitis	Neostomy	3.4	5.7	41	603
				4.1	6.3	32	590
31	57	Cancer of stomach	Resection	3.5	5.9	32	699
				3.4	6.5	28	604
				3.3	5.5	25	605
32	32	Acute appendicitis	Drainage	4.1	5.5	44	602
33	57	Cancer of stomach	Resection; anterior gastro-enterostomy	...	5.5	26	676
				3.9	4.9	36	708
34	57	Cancer of colon	Resection	3.4	5.3	39	527
				2.5	5.1	..	528
				3.1	4.8	..	646
				3.1	4.3	46	583

TABLE 3.—*Summary of Fluid and Salt Administration in Cases of Gastric and Intestinal Surgery*

Cases of Gastric Diseases, 14; Cases with Edema, 11	
Average daily fluid intake (total) for 5 days.....	3,153 cc.
Average daily fluid containing sodium chloride (0.9% NaCl).....	1,718 cc.
Average daily sodium chloride intake.....	15.5 Gm.
Average serum protein at time edema noted (range, 3.7-5.8).....	5.2 Gm. per 100 cc.
Cases of Acute Appendicitis with Drainage, 6; Cases with Edema, 5	
Average daily fluid intake (total) for 5 days.....	2,619 cc.
Average daily fluid containing sodium chloride (0.9% NaCl).....	2,170 cc.
Average daily sodium chloride intake.....	19.5 Gm.
Average serum protein at time edema noted (range, 5.2-5.5).....	5.4 Gm. per 100 cc.

eases exceeded 3,000 cc. This included the fluid intake by all routes, but by intravenous or subpectoral routes 1,700 cc. was given daily, with a salt content of over 15 Gm. The average daily intake of sodium chloride for a normal person does not exceed from 5 to 6 Gm. a day. A glance at table 1 will suffice to indicate that in only an exceptional case were the blood chlorides below a normal level, and in many instances the figures were abnormally high as a direct result of the administration of sodium chloride. That the amount of sodium chloride given was in excess is also indicated by the abnormally high

urinary specific gravities which ranged between 1.015 and 1.040, with an average about 1.030, in spite of a very adequate fluid output. In some instances there was an associated oliguria, but in many instances there was a good urinary output even in the presence of edema.

In the group of patients with gastroduodenal disease there would seem little reasonable doubt that the situation immediately preceding surgical intervention plus the necessary limitation of all food and an excessive administration of salt and water were the factors involved in the production of edema. The average amount of serum protein noted at the time of the development of edema was 5.2 Gm. per hundred cubic centimeters, which is well below the critical level for the development of edema. The range was between 3.7 and 5.8 Gm. in these cases during the period of edema. The lowering of the serum protein was due first to malnutrition, and second to subsequent dilution of the plasma by excessive amounts of fluid. It would seem that the retention of water in the tissues was dependent on the altered osmotic relations as a result of the foregoing factor, plus the addition of excessive amounts of sodium chloride, resulting in a movement of sodium to the tissues along with water. Such an hypothesis is in accord with the results obtained in numerous experimental observations.<sup>2</sup>

The accompanying chart, presenting findings in case 11, shows graphically what has just been discussed. The protocol of the case indicates that the factors of preceding malnutrition, postoperative starvation and the excessive administration of fluid and salt were all present. Prior to operation the serum protein was apparently at a normal level (6.2 Gm. per hundred cubic centimeters). Such an apparently normal figure is not uncommon in association with dehydration, and may give a false sense of security. Once a slight excess of fluid has been given, the serum protein drops rapidly, as actually happened in this instance. Postoperatively, 21,300 cc. of fluid was given in the first six days, with a total salt content of 147 Gm. Under this regimen the serum protein dropped in four days to a level of 5.2 Gm. per hundred cubic centimeters, and in spite of a marked change in therapy it reached a low level of 4.4 Gm. in four more days. The effect of the administration of such large amounts of salt is reflected in a rise in blood chlorides from a level of 505 mg. per hundred cubic centimeters to one of 610 mg. in four days. Edema of the extremities was noted two days after operation and continued to increase until anasarca was present. This coincided with the lowest figure for serum protein, and in the

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2. (a) Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis. *J. Clin. Investigation* 8:337, 1930. (b) Falta, W., and Quittner, M.: Ueber den Chemismus verschiedener Oedemformen. *Wien. klin. Wochschr.* 30:1189, 1917. (c) Footnote 1.



face of a beginning diuresis brought about by a sharp restriction of fluids. As soon as diuresis was established, the edema disappeared rapidly and the serum protein rose. At the time of the second operation jejunostomy was performed, and an adequate protein and salt intake was possible. Vomiting recurred, however, in a few days, and attempts to maintain an equilibrium were not possible. The final drop in chlorides and serum protein was the result of excessive vomiting and diarrhea with resultant loss of fluid, protein and salts.

In the patients (cases 15 to 19 and 32) who developed either visible or "potential" edema following an operation for appendicitis, the factors involved are not quite so clear. There was obviously no question of undernutrition before operation. All the patients had essentially irrelevant histories before the attack of appendicitis and were well nourished. Following operation the excessive administration of fluids and sodium chlorides was as striking as in the first group of cases. The average daily fluid intake for the first five days after operation was approximately 2,600 cc., of which 2,100 cc. was given intravenously or by clysis, with a total sodium chloride content of almost 20 Gm. a day. It is quite possible that an intake of over 2.5 liters of fluid was advisable in view of the elevation of temperature with consequent loss of water but there is little reason to warrant the administration of over 19 Gm. of salt a day for nearly a week. It will be noted that the serum protein dropped to a critical level or below in all of the cases observed. In case 19 no determinations were made, but as it differed in no way from the other five cases it is reasonable to assume that here also there was a similar reduction in serum protein. It is possible that the lowering of the serum protein was due solely to dilution by excessive fluid, especially by the intravenous route. Experimental work by Beard and Blalock<sup>3</sup> would indicate that this may be a partial explanation of this phenomena. The edema noted in these patients was not due to local inflammatory changes in the tissue, and changes in the serum protein obviously were not due to such a cause. There are two other possible factors which may have contributed to the lowering of the serum protein and the development of edema. In each instance, because of the localized peritonitis associated with a gangrenous appendix, drainage was necessarily established and was profuse. Here then was a cause for the lowering of serum protein, namely, loss of serum protein by actual drainage. Whether a coincidence or not, my associates and I have not observed edema in

3. Beard, J. W., and Blalock, A.: Intravenous Injections: A Study of the Composition of the Blood During Continuous Trauma to the Intestines When No Fluid is Injected and When Fluid is Injected Continuously, *J. Clin. Investigation* **11**:249, 1932; The Effects on the Composition of the Blood of the Subcutaneous Injection of Normal Salt Solution into Normal Dogs and into Dogs Subjected to Intestinal Trauma, Graded Hemorrhages and Histamine Injection, *ibid.* **11**:311, 1932.

cases of simple appendicitis not needing prolonged drainage. Our own animal experiments now under way would seem to indicate that drainage alone, even in the absence of sepsis, will apparently act as a factor in lowering the protein content of the blood and in the development of edema. In addition, it is conceivable that sepsis, even if localized and properly drained, may cause a greater generalized capillary permeability with the escape of fluid into the tissues. In this group of cases, then, excessive fluid and salt intake, plus loss of protein by drainage, and the possible influence of sepsis on capillary permeability must be considered as the causes of the occurrence of tissue edema. In cases 21 and 25 the loss of protein by drainage probably constituted a real factor in the development of edema. The former case was that of a patient with a draining abscess of the lung, and the latter that of a patient with a draining septic hip.

It is of interest to comment on certain other aspects of the problem as illustrated in some of the foregoing cases. In case 25 undernutrition from chronic sepsis of the joint in association with a marked anemia formed the background of the clinical picture. Following operation on the hip, anorexia became more marked and the anemia increased. A transfusion was indicated and was performed, but was followed by a severe reaction with polyuria, hematuria, jaundice and a subsequent uremic picture. Edema undoubtedly developed because of an underlying severe inanition, coupled with inability of the kidneys to excrete water and salt properly. The serum protein was already at a critical level of 5.5 Gm. per hundred cubic centimeters. In view of the very high amount of nonprotein nitrogen (195 mg. per hundred cubic centimeters) and extreme dehydration, fluids had to be pushed and the edema increased, as was to be expected, coincident with a reduction in the serum protein to 4.4 Gm. per hundred cubic centimeters. Before a diuresis was finally established, anasarca had developed with so much pulmonary edema that the outcome was extremely problematic. Persistent vomiting made it impossible to supply sufficient protein in the diet to raise the serum protein, and further transfusions for the sole purpose of raising the serum protein were refused. Fortunately a diuresis was finally established by the use of salyrgan, and subsequently the edema disappeared with a complete return to normal of the blood values and a complete restoration of kidney function. In this case the mechanism of edema formation was complicated by temporarily disturbed renal function, although the background was essentially that of inanition. As previously noted, drainage from the septic hip may have been an additional factor.

In case 26 the mechanism for the production of edema differed from the preceding cases and is of some interest. As indicated in the case report, no element of undernutrition was present. Three factors seemed to combine toward the lowering of the serum protein and the

accumulation of fluid in the tissues. In the first place there was a tremendous loss of protein associated with a hemorrhage from a duodenal ulcer severe enough to cause the red count to drop to about 1,000,000 cells per cubic millimeter in a few days. This represented an actual loss, only to be replaced by a proper protein intake or by transfusion. The former was impossible because of continued bleeding. The latter was tried, but unfortunately was followed by a fairly severe reaction with some resultant disturbance of kidney function. In addition, during the period preceding the development of edema, the patient received alkalis in the form of powders made up of sodium bicarbonate and calcium carbonate or magnesium oxide. Because of the temporary impairment of renal function, alkali was retained to such an extent that an actual alkalosis developed. In this case the serum protein was lowered primarily by loss through hemorrhage. Alkalosis and renal dysfunction provided the other factors necessary for an accumulation of fluid in the tissues. Diuresis was finally produced by the omission of alkalis and by an increase in the intake of protein by mouth. This case is of additional interest because of the possibility of surgical intervention. Although surgical intervention immediately after a large hemorrhage from a duodenal ulcer is not usually indicated, continued bleeding occasionally necessitates an operation. Under such circumstances the administration of fluids and salt that is normally consequent on gastro-intestinal surgical procedures might conceivably have resulted in edema of even more serious import.

That the finding of a normal amount of serum protein before operation does not constitute a guarantee against the development of edema was noted in several cases, and is best exemplified in case 14. This patient had a typical story of pyloric obstruction from carcinoma, was underweight and dehydrated. An operation, posterior gastro-enterostomy was decided on, and blood studies were made with a view to determining the optimum administration of fluids and salt. The serum protein was 7.2 Gm. per hundred cubic centimeters, non-protein nitrogen 43 mg. and blood chlorides, 506 mg. In view of the normal serum protein, the slightly elevated nonprotein nitrogen and the low chlorides, it was decided to administer a reasonable quantity of physiologic solution of sodium chloride intravenously during the first few days after operation. For the first eight days an average amount of 1,070 cc. of fluid was given intravenously, with an average daily salt intake of 8.5 Gm. In spite of the rather moderate amounts used, edema developed in eight days and was accompanied by a lowering of the serum protein to 5.5 Gm. per hundred cubic centimeters. Intravenous injections were at once omitted, and the edema disappeared immediately with an associated rise in serum protein to the original level of 7.3 Gm. per hundred cubic centimeters. The carcinomatous process was so widespread that the gastro-enterostomy did not func-

tion satisfactorily, with the result that vomiting persisted, dehydration rapidly returned and death ensued shortly thereafter. As long as intravenous administration of fluids was withheld, the serum protein did not drop again and edema did not develop, regardless of the rapidly advancing starvation. In other words, the normal level of serum protein gave a false idea of the protein content of the tissues and blood, and was lowered rapidly with the administration of fluids. Our own recent experiments have repeatedly borne out the fact that long continued undernutrition, especially with protein deficiency, may be associated with a normal or high figure for serum protein without the development of edema, unless sufficient amounts of fluids and salt are simultaneously administered. Peters<sup>4</sup> has noted such a possibility.

From the foregoing discussion it is evident, we think, that the important factors concerned in the development of nutritional edema after surgical operation are first an underlying condition of undernutrition, although this is not essential, as shown in the cases of appendicitis. In addition, there must be an actual lowering of the serum protein to a critical level by the administration of a somewhat excessive amount of fluid. The administration of sodium chloride or alkaline salts tends to increase the retention of fluids by the tissues. The serum protein may also be lowered by actual loss of blood from hemorrhage. Profuse drainage may accomplish a similar result. Retention of fluid and salt may be further aggravated by temporary renal dysfunction following some such phenomenon as a severe reaction to transfusion. Obviously the food intake after an abdominal operation is limited, and particularly in protein, thus constituting an added factor in the continued maintenance of a low level of serum protein.

In addition to the foregoing considerations, it is important to comment on certain other aspects of the question.

It is obvious from the preceding discussion that in spite of an apparently normal level of serum protein edema may be produced rapidly by the administration of amounts of salt-containing fluid that would ordinarily cause no trouble. The underlying factors of extreme malnutrition and dehydration must, however, be a fundamental background for such an occurrence. It remains to ask what is the actual critical level for serum protein at which edema begins to develop. Van Slyke<sup>2a</sup> and others have apparently shown that a level of  $5.5 \pm 0.3$  Gm. per hundred cubic centimeters constitutes the point where fluid begins to leave the blood and accumulates in the tissues. Serum albumin likewise must fall below a level of  $2.5 \pm 0.2$  Gm. per 100 cubic centimeters before edema develops. Examination of our figures

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4. Peters, J. P.; Bruckman, F. S.; Eisenman, H. J.; Hald, P. M., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VII. A Note on the Proteins in Acute Nephritis, *J. Clin. Investigation* **11**:97, 1932.

indicates that these figures apply for the most part. Although the actual figures were undoubtedly not obtained at the moment edema began to occur, in most instances the time relation between the two was fairly close. In nearly every instance the serum protein was at or below the so-called critical level when edema was noted. An interesting fact may be noted in case 23. In this patient the serum protein was on numerous occasions below 3.5 Gm. without any associated edema. In this case an intractable diarrhea prevented sufficient absorption of water to occur to permit the development of edema even in the presence of an extremely low amount of serum protein, again emphasizing the importance of other factors than malnutrition alone. This was also the case in the terminal stages of case 11 in which the serum protein dropped to 4.4 Gm. per hundred cubic centimeters without the recurrence of edema.

From our observations one cannot determine whether the intravenous administration of fluid and salt causes a greater tendency to edema than rectal administration. It probably is true that either of these routes will aid in the development of edema more quickly than the oral or rectal administration. It is also true that postoperatively the two former methods are of necessity the methods of choice for the maintenance of an adequate prolonged fluid intake. Some experimental work<sup>3</sup> would indicate that intravenous administration of fluid causes a more rapid drop in serum protein and a correspondingly more rapid passing of fluid into the tissues.

It is of some interest that in at least two instances the finding of pulmonary edema was the first indication of an abnormal retention of fluids in the tissues, although in most instances the dependent portions of the body and the extremities were the first to show edema.

It is obvious that in most instances the development of edema did not per se constitute a grave danger. In several instances, however, it apparently retarded the normal functioning of a gastro-enterostomy and rendered convalescence longer and more unpleasant because of vomiting. It may be that this is a not too uncommon cause of poorly functioning gastro-enterostomies during the immediate postoperative period. In one instance death was undoubtedly caused directly by partial intestinal obstruction due to edema of the intestinal wall. Oxygen therapy was considered necessary in two instances because of extreme pulmonary edema. The avoidance of such postoperative edema is obviously desirable. A limitation of the quantity of fluids and salt administered in cases showing definite malnutrition before operation would seem a logical corollary. In addition, preliminary determinations of serum protein and chlorides would serve as a partial indication for such limitations. In extremely undernourished patients a preliminary gastrojejunostomy might well be advised in order to permit a satisfactory protein intake for some days until the serum protein had

been raised above the critical level. Milk, egg albumin and gelatin are the most easily utilized foods for such a purpose. If intestinal edema develops after a surgical procedure, it may be combated either by attempting to raise the serum protein by limiting the intake of water and salt or alkali, or by producing a diuresis. When it is impossible to feed large amounts of protein, repeated transfusions are of some immediate benefit and should be considered even in the absence of anemia. Transfusion of plasma alone would be the most advantageous, if such a procedure could be carried out. The most efficient methods of producing a diuresis consist in the administration of the mercurial diuretics intravenously, or by the intravenous administration of very concentrated solutions of dextrose. Digitalis is of no value. As all the foregoing measures for the treatment of edema after it has developed demand intensive and sometimes rather heroic action, preventive measures are much to be desired. This is especially true because of the possible avoidance of postoperative complications and a shortening of convalescence, and also because of a possible reduction in operative mortality.

#### SUMMARY

1. Data on thirty-four patients who developed a critically low amount of serum protein following routine surgical procedures are presented. Some degree of edema was present in most of them.

2. It is suggested that usually such low values for serum protein and the consequent edema are the result of undernutrition, which may take place both before and after operation. The reduction in the intake of protein is probably the most important element in their pathogenesis.

3. Additional factors in the production of these complications may be the administration of excessive amounts of fluid and salt after operation, especially by the intravenous route, profuse surgical drainage, the general effects of sepsis, loss of serum protein by massive hemorrhage and a retention of base due to temporary disturbance of renal function.

4. The possibility has been noted of the occurrence of edema, even in the presence of apparently normal values for serum protein.

5. The possibility of a nutritional edema of the intestinal wall as a cause of a poorly functioning gastro-enterostomy has been discussed, and the suggestion has been made of the advisability of performing a preliminary jejunostomy for feeding purposes in patients who are obviously undernourished and who require major gastric surgical procedures.

6. The treatment of the complication of postoperative edema has been discussed.

# DIAGNOSIS OF SURGICAL TUBERCULOSIS

## COMPARISON OF DIAGNOSIS BY INOCULATION OF GUINEA-PIGS AND BY CULTURE

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In recent years the use of culture methods for the isolation of tubercle bacilli in the diagnosis of tuberculosis has received considerable attention. Several methods have been proposed for the isolation of tubercle bacilli, the majority being based on procedures designed to eliminate possible contaminants and to supply the peculiar nutritive requirements of the tubercle bacillus. Thus, the methods of Hohn,<sup>1</sup> Petragani,<sup>2</sup> Miraglia<sup>3</sup> and Loewenstein<sup>4</sup> have been employed in various European laboratories, while the procedures devised by Petroff,<sup>5</sup> Corper and Uyei,<sup>6</sup> Sweany and Evanoff<sup>7</sup> and others have received attention in this country.

Corper and Uyei studied the relative efficiency of various alkalis and acids in destroying contaminants in tuberculous materials. They concluded that acids, as recommended by Loewenstein, were superior to alkalis, and of the former, sulphuric acid gave the best results in their first series of tests. Based on this, they first proposed a method of cultivation of tubercle bacilli from tuberculous materials, which involved treatment of the material with an equal volume of 6 per cent sulphuric acid at 37 C. for thirty minutes, concentration by centrifugation and inoculation of the sediment onto crystal violet-potato slants. Crystal violet, certified by the Commission on the Standardization of Biological Stains, was used as a bacteriostatic agent to inhibit growth of contaminations. A small amount of glycerin broth was placed in the bottom of each tube. Corper and Uyei later found that glycerin water could be

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From the Laboratory Division, Hospital for Joint Diseases.

1. Hohn, J.: *Zentralbl. f. Bakt. (Abt. 1)* **121**:488, 1931.
2. Petragani, G.: *Atti Accad. fisiocrit.* **1**:173, 1926.
3. Miraglia, M.: *Pediatrics* **37**:1167, 1929.
4. Loewenstein, E.: *Wien. klin. Wchnschr.* **37**:231, 1924.
5. Petroff, S. A.: *J. Exper. Med.* **21**:38, 1915.
6. Corper, H. J., and Uyei, N.: *J. Lab. & Clin. Med.* **13**:469 (Feb.) 1923; **14**:393 (Feb.) 1929.
7. Sweany, H. C., and Evanoff, M.: *Am. Rev. Tuberc.* **17**:47 (Jan.) 1923; **18**:661 (Nov.) 1928; **20**:227 (Aug.) 1929.

used in place of the glycerin broth.<sup>8</sup> They further modified their technic by the substitution of 5 per cent oxalic acid for the sulphuric acid used in the preliminary treatment of the material to be cultured.<sup>9</sup> They reported that when oxalic acid was used, a greater proportion of the tubes inoculated gave growth, and there was an appreciable reduction in the number of contaminations.

The possibilities of the application of the culture method to clinical material led us to institute a comparative study of inoculation of guinea-pigs and the method of Corper and Uyei in the laboratory diagnosis of tuberculosis.

#### EXPERIMENTAL DATA

*Technic.*—About two thirds of the specimens used were treated with sulphuric acid, as first described by Corper and Uyei, and one-third with oxalic acid. Our technic, based on that of Corper and Uyei, is as follows:

Five per cent oxalic acid (6 per cent sulphuric acid in the earlier tests) was the reagent employed to destroy contaminants. The potato tubes consisted of the usual potato cylinder slants which had been soaked for from one to two hours in 1 per cent sodium carbonate containing 1:100,000 certified crystal violet. In the bottom of the potato tubes was placed 2 cc. of 5 per cent glycerin water. Equal volumes of the acid reagent and the material to be examined were placed in a 15 cc. centrifuge tube, mixed thoroughly by shaking, and incubated at 37 C. for thirty minutes. Ten cubic centimeters of sterile salt solution (0.85 per cent) was then added; the mixture was shaken and concentrated by centrifugation. Smears of the sediment, stained by the Ziehl-Neelsen method, were always examined before the sediment was cultured or injected into a guinea-pig. It is interesting to note that tubercle bacilli were rarely found in smears of the specimens used. The sediment was inoculated onto four potato slants. The tubes were sealed with sealing wax and incubated at 37 C. Tissues to be cultured were first ground in a Rosenow tissue crusher and suspended in a few cubic centimeters of sterile saline. The suspension was then treated like a fluid specimen, as previously described. The method was used with pus, urine, synovial fluid, tissues, pleural fluid, sputum and feces.

The sediment obtained as described was divided into two portions, one portion being used for culture and the other for inoculation. The guinea-pigs were inoculated subcutaneously in the right axilla. The animals were fed on an adequate diet and kept in individual cages in clean quarters.

After incubation of the cultures for fourteen days without opening, they were examined at intervals of one week, individual smears being made from each tube and stained by the Ziehl-Neelsen method (steaming in fuchsin for ten minutes). As soon as typical acid-fast bacilli were found in one or more smears from a culture, the guinea-pig inoculated with the same material was killed and autopsy performed. If an abscess or necrotic tissue was present at the site of inoculation, smears were made and examined for acid-fast bacilli. Portions of the liver, spleen and lymphatic tissue at the point of inoculation were taken in a diluted solution of formaldehyde, U. S. P. (1:10) for histologic examination. The cultures were

8. Corper, H. J., and Uyei, N.: Simple Glycerol Water-Crystal Violet Potato Cylinder Medium for Diagnostic Cultures of Tubercle Bacilli, *Arch. Path.* 7:835 (May) 1929.

9. Corper, H. J., and Uyei, N.: *J. Lab. & Clin. Med.* 15:348 (Jan.) 1930.



returned to the incubator, to remain until a satisfactory growth had occurred. As long as cultures were negative on repeated smears, they were examined at weekly intervals for six weeks. If negative at this time, they were held in the incubator for four weeks longer, being examined weekly for visible growth. At ten weeks, after final smears were made and examined, the cultures were discarded, and autopsy was performed on the guinea-pigs. Even though no gross lesions were found at autopsy, the liver, spleen and tissue at the point of inoculation were taken for histologic examination. This is a routine procedure in this laboratory. Only after such examination of cultures and of sections of tissue from the guinea-pigs was a specimen considered to be nontuberculous.

*Results with Specimens from Nontuberculous Cases.*—One hundred and six specimens were studied. These were distributed as follows: synovial fluid, sixty-two; urine, twenty-two; pus, ten; tissue, four; pleural fluid, five; hydrocele fluid, sputum and stool, one each. Of the specimens of synovial fluid, forty-one were from cases of the various nontuberculous arthritides, sixteen from cases of synovitis, two from cases of bursitis and one each from a case of popliteal cyst, a possible endothelioma of the distal end of the femur and a case of osteochondritis dissecans. The twenty-two specimens of urine were from sixteen patients, urine from both the right and the left kidney of six patients being cultured. Eighteen specimens of urine were obtained by cystoscope, and four were specimens from the bladder. The specimens of pus were from various abscesses and sinuses. The tissues represented material taken for biopsy—lymph glands and tissue from joints. The specimens of pleural fluid came from cases of pleurisy with effusion, simple pleural effusion and neoplasm of the lung. All of the specimens used had been sent to the laboratory for routine inoculation into guinea-pigs, in many instances to rule out the possibility of tuberculous infection.

As indicated previously, cultures of these materials were incubated for ten weeks; smears were made weekly for six weeks, and again at ten weeks. Autopsy was performed on the guinea-pigs at the end of ten weeks, and sections of their tissues were studied, before they were considered to be nontuberculous. Final confirmation of the nontuberculous nature of each specimen was obtained by a study of the individual histories, all available diagnostic criteria being taken into consideration.

The results of the culture and inoculation in these one hundred and six parallel tests checked in all except ten cases, in which they were obscured either by the premature death of the guinea-pigs or by accident to the cultures. Five guinea-pigs died of intercurrent infection within a short time after inoculation. In all cases the corresponding cultures were sterile at the end of ten weeks. Of the remaining five instances in which the parallel tests could not be compared, all four tubes in each of three cultures became contaminated from one to four weeks after inoculation. Two other cultures were destroyed at three weeks when a

faulty thermostat caused the temperature of the incubator to rise to 55 C. over a week-end. In these five cases, at the end of ten weeks, gross and histologic examinations of the corresponding guinea-pigs gave negative results.

In summary, therefore, agreement of the results was obtained in ninety-six of the nontuberculous specimens. In ten additional cases one or the other of the two methods failed, so that comparison was not possible. However, in these ten instances presumptive evidence of the nontuberculous nature of the material under examination was obtained by one method, even though the parallel test could not be used for comparison. In no case was the parallel result lost because of the failure of both tests to be carried to completion.

*Results with Specimens from Tuberculous Cases.*—A total of forty-four specimens from forty-two tuberculous subjects was cultured. The distribution of these was: synovial fluid, eighteen; pus, eighteen; urine, six, and tissue, two. Of the specimens of synovial fluids, fifteen were from the knee joints, and one each from the elbow, shoulder and hip joints. The pus was obtained from various abscesses and sinuses, the majority being associated with infections of the bone or joint. Five specimens of urine were obtained by cystoscope; one was a specimen from the bladder. From one patient, urine from both the right and the left kidney was cultured. Both specimens of tissue came from ankle joints.

Thirty-four specimens, from thirty-two persons, yielded cultures of tubercle bacilli. As indicated previously, the cultures were examined by smears of all tubes at weekly intervals until the smears revealed the presence of typical acid-fast bacilli. Twelve cultures were first positive at two weeks, seven at three weeks, six at four weeks, four at five weeks, three at six weeks and one each at seven and ten weeks. In a few cases, at various time intervals from two to ten weeks, the positive smear coincided with the appearance of macroscopic growth, although as a rule the visible growth did not appear until later. A positive diagnosis having been made by smear, the tubes were held in the incubator until a satisfactory growth occurred, when they were placed in stock. For diagnosis, Corper and Uyei waited until macroscopic growth appeared in their culture tubes; in the majority of cases this occurred at about the fourth or fifth week, although at two weeks growth was sometimes visible. It would seem that the earlier examination by smear possesses a distinct advantage in that the time of arriving at a diagnosis is shortened materially, without any appreciable sacrifice of accuracy.

When the cultures were positive by smear, the guinea-pigs were killed and autopsy performed, tissues being taken for histologic examination. Occasionally no gross change was found in the axilla, particularly when the guinea-pig was killed at two or three weeks after

inoculation. Usually there was a small nodule, with or without a caseous center, and in some instances there was only a mass of necrotic tissue, with no focus therein. Smears were made from the necrotic tissue or from an abscess, when present. The smears generally revealed the presence of acid-fast bacilli, but often they were rare and were found only after prolonged search. Abscesses, when present, were small, and sometimes palpable, at the time the animal was killed, but of themselves were not sufficient for diagnosis.

We found that guinea-pigs killed from two to four weeks after inoculation (when the cultures were positive) showed no gross tubercles in the liver or spleen in about half of the instances. Likewise, histologic examination of sections from the liver and spleen was negative for tubercles. Indefinite "tubercle-like" bodies were sometimes reported, but these were not definite enough to make a diagnosis of tuberculosis on the tissues. The diagnosis in these cases was definitely established by the positive culture.

On the other hand, when the cultures first became positive five or more weeks after inoculation, guinea-pigs killed at this time invariably showed gross evidence of tuberculous infection at autopsy, which was confirmed by histologic examination. In all of these, well developed abscesses containing acid-fast bacilli were found at the point of inoculation.

In ten of the tuberculous cases the cultures remained sterile for ten weeks. The corresponding guinea-pigs in five of these showed tuberculosis on gross and microscopic examinations. One was further confirmed when a surgical specimen removed some months later showed the presence of tuberculosis.

In three other cases, inoculation into the guinea-pigs gave negative results for tuberculosis and the cultures were also negative. Aspirated material from three persons with tuberculosis of the knee was used for culture and inoculation. Subsequently, tissue removed surgically from the knee joints of these three patients was shown histologically to be tuberculous, and the clinical course in these cases further confirmed the pathologic diagnosis.

Of still greater interest is a case of tuberculosis of an ankle in a woman 42 years of age. In January, 1929, she developed acute pain with swelling in the ankle, which after six months became more severe. After that, on two occasions, specimens were removed from the tissues of the joint which showed histologically typical tuberculosis. Tissue removed at the second, or fusion, operation was ground in a tissue crusher and prepared by Corper's technic. Cultures made from this prepared specimen were sterile after incubation for ten weeks. Likewise, the liver and spleen of a guinea-pig inoculated with a portion of the same specimen were negative for tuberculosis, grossly and micro-

scopically. However, at the autopsy of the guinea-pig there was a small encapsulated cystic mass in the axilla, containing a milky fluid, in which numerous acid-fast bacilli were demonstrated by smear. Culture of this fluid remained sterile indefinitely. The question arises in this case whether the organisms may not be avirulent for the guinea-pig, the local lesion becoming heavily encapsulated, while they still are capable of producing lesions in human tissues. Furthermore, an artificial environment appears to be unsuitable for their growth.

In this connection, the guinea-pig inoculated with one of the thirty-four positive cultures previously mentioned failed to develop generalized tuberculosis, with involvement of the liver and spleen, after six weeks. However, tubercle bacilli were found in the axillary abscess, which yielded a satisfactory growth on culture. The original culture when inoculated into a guinea-pig killed the animal in thirteen weeks.

Finally, one case is included of a man with a lesion of the lumbar vertebrae, which had all the clinical and roentgenologic appearance of Pott's disease. Two surgical specimens were submitted from the sinus tract, both of which showed chronic inflammation, but no evidence of tuberculosis. In addition, three guinea-pigs were inoculated with pus discharging from the sinus, one of these specimens also being cultured by Corper's method. The cultures and tissues from the guinea-pigs failed to reveal either tubercle bacilli or evidence of tuberculous infection.

Comparison as to agreement of all cultures and inoculations cannot be made in this tuberculous series, because the animals were killed as soon as the cultures became positive. When the cultures became positive within from two to four weeks, the absence of tubercles in the liver and spleen merely indicated the lack of dissemination of the infection, as tubercle bacilli were usually found at the point of inoculation. However, there was actual disagreement of results of the two methods in five instances, in which cultures were sterile after incubation for ten weeks, while gross and histologic examinations of the corresponding guinea-pigs revealed tuberculosis. We have had no instance in which the culture became positive, while the guinea-pig failed to show tubercles in the liver and spleen, or tubercle bacilli in the axilla after six weeks. Furthermore, it is of interest to note that in no instance was it impossible to arrive at a definite final diagnosis because of the loss both of the animal and of the cultures.

*Contamination of Cultures.*—As an important feature of the culture method is the use of reagents to destroy contaminating organisms or to inhibit their growth, mention of the incidence of contaminated cultures in this series is of interest. A total of six hundred tubes, representing one hundred and fifty specimens, was inoculated. One hundred and eighty-five, or 30.8 per cent, became contaminated. In practically every instance the contaminating organism was a mold. We found that the

inoculation. Usually there was a small nodule, with or without a caseous center, and in some instances there was only a mass of necrotic tissue, with no focus therein. Smears were made from the necrotic tissue or from an abscess, when present. The smears generally revealed the presence of acid-fast bacilli, but often they were rare and were found only after prolonged search. Abscesses, when present, were small, and sometimes palpable, at the time the animal was killed, but of themselves were not sufficient for diagnosis.

We found that guinea-pigs killed from two to four weeks after inoculation (when the cultures were positive) showed no gross tubercles in the liver or spleen in about half of the instances. Likewise, histologic examination of sections from the liver and spleen was negative for tubercles. Indefinite "tubercle-like" bodies were sometimes reported, but these were not definite enough to make a diagnosis of tuberculosis on the tissues. The diagnosis in these cases was definitely established by the positive culture.

On the other hand, when the cultures first became positive five or more weeks after inoculation, guinea-pigs killed at this time invariably showed gross evidence of tuberculous infection at autopsy, which was confirmed by histologic examination. In all of these, well developed abscesses containing acid-fast bacilli were found at the point of inoculation.

In ten of the tuberculous cases the cultures remained sterile for ten weeks. The corresponding guinea-pigs in five of these showed tuberculosis on gross and microscopic examinations. One was further confirmed when a surgical specimen removed some months later showed the presence of tuberculosis.

In three other cases, inoculation into the guinea-pigs gave negative results for tuberculosis and the cultures were also negative. Aspirated material from three persons with tuberculosis of the knee was used for culture and inoculation. Subsequently, tissue removed surgically from the knee joints of these three patients was shown histologically to be tuberculous, and the clinical course in these cases further confirmed the pathologic diagnosis.

Of still greater interest is a case of tuberculosis of an ankle in a woman 42 years of age. In January, 1929, she developed acute pain with swelling in the ankle, which after six months became more severe. After that, on two occasions, specimens were removed from the tissues of the joint which showed histologically typical tuberculosis. Tissue removed at the second, or fusion, operation was ground in a tissue crusher and prepared by Corper's technic. Cultures made from this prepared specimen were sterile after incubation for ten weeks. Likewise, the liver and spleen of a guinea-pig inoculated with a portion of the same specimen were negative for tuberculosis, grossly and micro-

scopically. However, at the autopsy of the guinea-pig there was a small encapsulated cystic mass in the axilla, containing a milky fluid, in which numerous acid-fast bacilli were demonstrated by smear. Culture of this fluid remained sterile indefinitely. The question arises in this case whether the organisms may not be avirulent for the guinea-pig, the local lesion becoming heavily encapsulated, while they still are capable of producing lesions in human tissues. Furthermore, an artificial environment appears to be unsuitable for their growth.

In this connection, the guinea-pig inoculated with one of the thirty-four positive cultures previously mentioned failed to develop generalized tuberculosis, with involvement of the liver and spleen, after six weeks. However, tubercle bacilli were found in the axillary abscess, which yielded a satisfactory growth on culture. The original culture when inoculated into a guinea-pig killed the animal in thirteen weeks.

Finally, one case is included of a man with a lesion of the lumbar vertebrae, which had all the clinical and roentgenologic appearance of Pott's disease. Two surgical specimens were submitted from the sinus tract, both of which showed chronic inflammation, but no evidence of tuberculosis. In addition, three guinea-pigs were inoculated with pus discharging from the sinus, one of these specimens also being cultured by Corper's method. The cultures and tissues from the guinea-pigs failed to reveal either tubercle bacilli or evidence of tuberculous infection.

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percentage of contamination occurring in the series treated with oxalic acid was appreciably lower than in the series treated with sulphuric acid. However, it must be remembered that our cultures were repeatedly opened for the purpose of making smears. Only a relatively few of the contaminations which occurred were found when the tubes were first examined at two weeks; thus they represent organisms which resisted the original acid treatment. The majority of contaminations occurred after the tubes had been opened one or more times. Hence we cannot ascribe the apparent difference in degree of contamination of the two series to the preliminary treatment.

In thirty-four cases in which positive cultures were obtained, a total of one hundred and thirty-six tubes was inoculated. Twenty-two tubes, or 16.1 per cent, became contaminated. Nearly 9 per cent of the contaminations occurred before cultures had become positive, and about 7 per cent after they were positive, as revealed by smear. However, these contaminations were so distributed that in nearly every instance two or three tubes remained uncontaminated, in which growth of tubercle bacilli eventually occurred. In only one instance was it impossible to obtain a stock culture, because all the tubes were eventually covered with mold.

The possibility of contamination may be a valid reason for allowing the cultures to remain unopened until a macroscopic growth occurs, rather than incur the risk of losing all cultures by the overgrowth of contaminating micro-organisms. This difficulty might be obviated by adding one or two tubes to each series of inoculations, which would be allowed to remain unopened during the entire period of observation. From our experience, the possibility of obtaining a positive diagnosis at the earliest opportunity outweighs the relatively infrequent loss of cultures because of contamination of all tubes of a series. Such loss by contamination of all tubes occurred fifteen times in our series of one hundred and fifty cases (10 per cent). This is a statistical percentage, however, and does not reveal what actually happened. Fourteen of these cases of loss occurred in the series treated with sulphuric acid, and only one in the series treated with oxalic acid. This is due, we believe, not to the method of preliminary treatment (since the tubes were repeatedly opened), but to the fact that the experience gained in handling the tubes of the first series resulted in the adoption of refinements in technic which yielded definitely fewer contaminations generally in the second series.

#### COMMENT

It is frequently important to arrive at a diagnosis earlier than is allowed by the ordinary inoculation of guinea-pigs. Corper and Uyei waited for the development of macroscopic growth in their cultures, which usually occurred in four or five weeks, and occasionally in two

weeks. We have shown that an early diagnosis by culture may be obtained by making smears of the cultures at a time when macroscopic growth has not yet occurred, and when the guinea-pig does not show any signs of tuberculous infection. We found that twenty-five of thirty-four cultures were positive at four weeks or less (twelve were positive at two weeks). On gross and histologic examination at this time, seventeen of the twenty-five guinea-pigs did not show tuberculosis, or at the most the condition was only suspected. When smears are positive, the cultures may be reincubated for the development of visible growth, which furnishes a positive check on the early diagnosis. The possession of cultures makes possible any further work desired, such as type differentiation.

Thus this study brings out the fact that there are two definite advantages in the cultural method of diagnosis. One is that, by weekly examination of smears from the cultures, it may often be possible to make an earlier diagnosis (from two to four weeks) than with the routine guinea-pig method. While this is so with the Corper method, it is quite likely that some other method, particularly one employing an egg medium, would give as satisfactory, if not better, results.<sup>10</sup> The other advantage of the culture method is that, should the guinea-pig die of intercurrent infection, the culture may remain to help establish a final diagnosis. Peculiarly enough, this was the case only with our nontuberculous material, in which five guinea-pigs died of intercurrent infection, while the cultures remained sterile during the entire period of observation.

Mention has been made of the occurrence of palpable abscesses in some of the animals soon after inoculation. While it is true that a lesion was present in the axilla which could be felt, and that tubercle bacilli (although frequently rare) could be demonstrated therein by smear when autopsy was performed, it must be remembered that the mere presence of an abscess in the axilla from two to four weeks after inoculation is not always indicative of tuberculous infection, and not a sufficient reason for killing the animal at this time. We have encountered a number of cases in which such an abscess persisted for some time after inoculation, due presumably to other micro-organisms, which were demonstrable by smears. These abscesses eventually disappeared, and the animals were shown ultimately by histologic section to be non-tuberculous.

On the whole, we feel that inoculation of animals cannot be supplanted by any culture method. In five of forty-four instances in our series (11.3 per cent), the guinea-pigs showed tuberculosis, while their

10. Feldman, W. H.: *Am. J. Clin. Path.* 1:285 (July) 1931. Hohn.<sup>1</sup> Sweany and Evanoff.<sup>7</sup>



corresponding cultures remained sterile for ten weeks. The inoculation method itself has many pitfalls, because of a number of factors which are difficult to control. The source of the material used for inoculation is highly important. We have obtained both positive cultures and disseminated tuberculosis in guinea-pigs with as little material as is contained on a swab introduced into a tuberculous focus. On the other hand, it is entirely possible to obtain, as previously indicated, synovial fluid from frank tuberculosis of the knee joint, which failed to produce tuberculosis in a guinea-pig or yield a growth of tubercle bacilli, while the tissue removed at biopsy was unmistakably tuberculous. Even in an open operation of a tuberculous focus, it is obvious that tissue may be removed which histologically will disclose tuberculosis, while another fragment sent to the laboratory for culture and inoculation may rarely contain no viable tubercle bacilli or no organisms sufficiently virulent to infect an animal.

It is striking that by the use of the two methods it was possible to arrive at a definite final diagnosis in all of the one hundred and fifty tests; this would have been impossible had only one of the tests been used exclusively. The use both of inoculation and of culture is to be preferred, since the loss of one may be compensated for by survival of the other test, and, as usually occurs, a check on the results is obtained when both tests are carried on to completion.

An outstanding fact in the discussion of the relative value of inoculation of animals and of the cultural method in the diagnosis of tuberculosis is the lack of agreement of the various writers on the subject. Corper and Uyei<sup>6</sup> believe that the cultural method is equal in efficiency to the guinea-pig test, and suggest that the cultural method may be substituted for inoculation. These conclusions were reached from a study of specimens of sputum and urine from persons with tuberculosis, and of tissues from animals experimentally infected with tuberculosis. Our own experience in handling material from clinical cases, such as are found in an institution in which many persons with bone and joint diseases are treated, certainly does not allow the acceptance of such a broad recommendation. If we were obliged to limit ourselves to but one method, we should prefer the guinea-pig test, on the basis of our present results.

Sweany and Evanoff,<sup>7</sup> with their culture mediums, reported somewhat better results by the cultural method than by the inoculation of guinea-pigs. They advocate the use both of cultures and of inoculation for diagnostic work, on the assumption that some organisms will grow well in cultures, while possessing too low a virulence for guinea-pigs, and that other strains will be pathogenic for animals, but will find the artificial environment of a culture medium unsuitable for growth. However, Feldman<sup>10</sup> also reported slightly better results with the inoculation

of guinea-pigs than with the various culture mediums which he used, namely, those of Corper and Uyei, Sweany and Evanoff, and Miraglia. Similar disagreement of opinion is found in reports of various European authors, some claiming the superiority of inoculation, and others reporting cultures to be at least equal to the guinea-pig tests.

An objection frequently raised to the guinea-pig method is the loss of animals by intercurrent infection. It may be pointed out that in this series only five guinea-pigs were lost for such a reason. In instances like these, the test is almost invariably a failure so far as concerns the arrival at a conclusion regarding tuberculous infection, for the animals usually die within a week after inoculation. Possibly inoculation subcutaneously into the axilla, as was done in this series, reduces the possibility of intercurrent infection. The small number of such infections in this reported series is entirely in accord with our usual results in the ordinary routine of the laboratory. Reasons for this, we believe, are found, not only in the site selected for inoculation, but in the fact that the animals are of a healthy stock, and are kept under good hygienic and feeding conditions.

We have pointed out that a careful examination of smears of the sediment obtained by the Corper concentration method rarely revealed the presence of acid-fast organisms. Since considerable time is often spent on such examinations with negative results, it appears that, for practical purposes, this preliminary examination might be omitted, particularly when applied to synovial fluid.

We make it a practice in this laboratory always to confirm the gross diagnosis on the liver and spleen of the guinea-pigs by histologic examinations of these tissues. Many laboratory workers feel that this is an unnecessary check. Others feel quite the opposite, stating that nontuberculous infections may be mistaken for tuberculosis on gross examination. Our own experience indicates that the gross examination checks satisfactorily with the microscopic. However, in spite of this, we have established the practice of making histologic examinations, since it adds little burden to the routine in a laboratory where tissues are constantly being examined.

#### SUMMARY AND CONCLUSIONS

One hundred and fifty specimens (one hundred and six nontuberculous and forty-four tuberculous) were studied in a series of parallel diagnostic tests, inoculation into guinea-pigs and the method of Corper and Uyei of cultivation on crystal violet glycerin water potato medium being used.

With ninety-six nontuberculous specimens, agreement of culture and animal inoculation was obtained. In ten instances no comparison of the results of the two methods could be made—five animals died of intercurrent infection, and five cultures were lost by contamination or accident.

In the tuberculous cases, disagreement occurred in five (11.3 per cent), in which the cultures were negative for tuberculosis, while gross and histologic examinations of the guinea-pigs gave positive results. This shows a definite balance in favor of inoculation of animals.

It was possible to arrive at a definite final diagnosis in all of the one hundred and fifty parallel tests—in the great majority of cases by agreement of both tests, and in a few either by inoculation of animals or by culture, while in no case were both animal and cultures lost. This could not have occurred had only one test been used exclusively.

Thirty-four cultures of tubercle bacilli were obtained from the tuberculous material. An early diagnosis (four weeks or less) was reached in twenty-five of these cases by making smears from the cultures; in these, at the time the smears first showed acid-fast bacilli, the cultures were macroscopically negative, and the guinea-pig at autopsy did not show tuberculosis, or it was only suspected.

While contaminations cannot be avoided, and probably are more frequent when cultures are opened at intervals for smears, the possibility of obtaining a diagnosis at the earliest opportunity appears to outweigh the relatively infrequent loss of all culture tubes of a series by contamination.

At the present time we do not believe that the cultural method should replace inoculation into animals in the diagnosis of tuberculosis. It appears to be preferable, however, to include both methods whenever possible. The one serves as a check on the other, while the double method provides a safeguard against possible loss—by intercurrent infection or contamination.

In the discussion a number of other features are considered concerning the laboratory diagnosis of tuberculosis.

The histologic checking of surgical and guinea-pig tissues was made by Dr. Henry L. Jaffe.

# BACKACHE; LUMBAGO; PAIN IN THE LOWER PART OF THE BACK

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More patients present themselves in the orthopedic department of the Stanford Clinics with backache than with any other complaint. It is frequent in private practice, and is a source of controversy in industrial accident work. Various pathologic entities have been advanced to account for it, some of them purely theoretical and, I believe, erroneous. To treat the symptom scientifically and indeed successfully one must be able to demonstrate definite facts which will account logically for the symptoms and clinical signs. Among the diagnoses which I have discarded as not satisfying these requirements are renal disease, prostatic hypertrophy, neuritis, muscular strain, faulty posture, myositis, fibrositis, fasciitis, radiculitis, rheumatism and pressure on the spinal nerves.

In order to clarify what follows I shall devote a few words to the anatomy of the bones and joints of this region. The bones are the three lower lumbar vertebrae, the sacrum and the two innominate bones.

The bodies of the vertebrae are connected to each other, and the body of the fifth lumbar vertebra is connected to the top of the sacrum, with which it makes a sharp angle, by the thick fibrocartilaginous disks. Between them there is no joint cavity, no synovial membrane. The lateral articulations are true joints, allow a small range of motion and possess a synovial membrane. The plane of the lateral articulation between the fourth and fifth vertebrae, like that of the lumbar articulations above it, is sagittal; that of the lateral articulation between the fifth lumbar vertebra and the sacrum is slightly oblique from the coronal. The coronal set of this articulation prevents the displacement forward of the fifth lumbar, to which its sharp angulation with the sacrum predisposes. The lateral articulations, like any other joints, are subject to sprains, i. e., tears of the capsule. The lateral masses of the fifth lumbar vertebra are large, and in the roentgenogram appear to impinge on the wings of the ilium, but in point of fact normally are separated from it by a good interval, as a glance at the skeleton will show.

The spinal foramina give egress to the spinal nerves, the roots of the sacral plexus. They are of such size and are so placed as to render untenable the assumption that the spinal nerves are ever compromised

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as they pass through the foramina. Indeed, if the spinal nerves ever were pressed on by bone in this situation, extensive and prolonged paralyses would result. These are not seen unless the cord itself is damaged by injury or disease.

The sacrum is wedged between the innominate bones like the keystone of an arch. The sacro-iliac is a true joint lined by irregular fibrocartilage. It possesses a limited range of motion, chiefly of rotation of the ilium. This rotation causes the pubes to move up or down. In heavy lifting, the sacrum is forced down between the ilia, spreading them apart. To demonstrate this, let one place a belt snugly about the pelvis just above the femoral trochanters, and then, bending forward, lift a heavy weight from the ground. If the belt is weak, it will break. Motion in the sacro-iliac joint lessens as age advances, and recent investigations show that in time the joint is often obliterated by bone.

"During pregnancy the pelvic joints and ligaments are relaxed, and capable therefore of more extensive movements" (Gray); hence, probably, the backaches of women during the child-bearing period. The pelvic joints are built for stability, not for mobility. When, during pregnancy, they allow a free motion, they are easily sprained, strained or even, as will be seen later, actually displaced. Of the truth of this statement any one can convince himself by applying a snug belt, *always below the anterior-superior spines of the ilium*, to women who complain of backache during pregnancy and after confinement.

#### THE SPECIFIC CAUSES OF BACKACHE

*Arthritis.*—Little need be said here as to the relation of cause and effect. While ideas of treatment may differ, if the clinical signs and the roentgenograms reveal the presence of a lumbar arthritis, the sequence of cause and effect is unmistakable. Let me repeat here that pressure on the spinal nerves plays no greater rôle in causing the pain in inflammation of the spinal joints than in inflammation in the other joints of the body. The cardinal symptoms and physical signs are the same in both, except that the depth of the spinal joints prevents one from observing swelling, heat or sensitiveness to pressure. The pain may be felt in the back alone, or it may be referred down the sciatic distribution. It is a true referred pain. When painful stimuli come in over a certain nerve tract, one refers them to the area from which one is accustomed to receive sensations over this tract, as a man whose leg has been amputated feels pain in his foot. Hence, if I have an inflammation in my lateral articulations, I may complain of typical sciatica.

The importance of the lateral articulations in spinal arthritis has, I believe, been overlooked. They should be studied in anatomic specimens. The roughnesses and irregularities, the "spurring" and "lipping,"

of second type arthritis, so frequently seen, explains adequately the lumbago and sciatica of middle-aged and elderly persons. Indeed, it is possible that these bony changes in the lateral articulations are much more important clinically than are the enormous spikes and ridges of the vertebral bodies on which physicians fix attention.

One thing is important in this connection: No constant relation exists in this type of arthritis between the amount of anatomic change and the clinical picture. A man with a minimal amount of spurring may complain of great pain, while the roentgenograms of the lumbar spine may reveal extensive damage in the joints of a man who does not complain of pain. The characteristic changes are often picked up as an accidental finding in roentgenograms of other organs. These joints, already damaged by the disease, are easily sprained. They are like any other damaged machine. If a man suffers a sudden pain in his back after lifting or falling, and the films show advanced changes in the bone on the same day, they must not be ascribed to the injury.

The treatment of the various forms of arthritis is still a matter of discussion, and I shall not enter into it here at length, but I shall reiterate what I have set forth on numerous occasions. Second type arthritis—degenerative arthritis, hypertrophic arthritis, osteo-arthritis, the arthritis deformans of the Germans, the arthritis characterized by lipping and spurring—is not caused by bacterial infection. All the evidence at one's disposal indicates that the cause is some living organism, not bacterial, which usually gains access to the body through the open bone at the roots of dead teeth. All the changes observed in the bones and joints in this form of arthritis are absolutely different from those caused by bacteria. Further laboratory studies, which I hope soon to publish, confirm the conclusion set forth years ago, that the primary pathologic change is an aseptic necrosis in the bone marrow near the joint. The arthritis which follows, that is, the inflammation in the synovial membrane, is essentially a traumatic arthritis, caused by the distortion of the end of the bone. It follows that any attempts to treat the disease by removal of infection in the tonsil or deep urethra, by the employment of so-called antirheumatic drugs, vaccines and elaborate physical therapy or by attention to the metabolism are doomed to disappointment. The same may be said for operations on the intestinal tract. Even diet is secondary. The supposititious causal organism is probably domiciled in the alimentary canal, and usually the patient with this form of arthritis feels better when his digestive system is in order. Hence he should eat the kind of food which agrees with him. The present fashion of weighing the carbohydrate metabolism reminds one of the Saulsbury treatment with rare beef and hot water, a fad of fifty years ago. A short time ago the important thing was purin metabolism.

One form of treatment which never loses its vogue might be called the ambulatory treatment. It consists in sending the patient to some one else who will cure by diet, irradiation, heat, electricity, massage, or other forms of therapy. Osteopathy, chiropractic and faith healing are on the same basis.

*Fracture.*—Fractures of the spine are often followed by persistent backache, especially if the vertebrae already have been damaged by a preexisting chronic arthritis. The pain may be localized or may be in the form of typical root pain. Sometimes it runs down the thighs as a sciatica. The diagnosis may be made tentatively from the history and from the symptoms and physical signs. A hump may or may not be present. Limitation of motion is the rule. The final diagnosis is established by the roentgenograms.

The most satisfactory treatment is by immobilization. For the milder pains, and especially for elderly persons, a light steel brace is perhaps the best. In younger persons the case is not so simple. Some authorities recommend treatment with a brace, continued for a long time on account of the notoriously slow healing of spinal fractures. I incline strongly to operation in any case of severe persistent pain after fracture, fusing the fractured vertebra with the one above and below it. This puts the damaged piece of machinery out of function. In fact, in any fresh crushing fracture without injury to the cord, in a healthy young person, I always urge operation. This might be regarded as the preventive treatment of backache.

*Spondylolisthesis.*—The acute angulation forward which the spine makes at the sacrolumbar articulation predisposes to the slipping forward of the fifth lumbar vertebra on the sacrum—spondylolisthesis—under stress. A sagittal plane to the lateral articulations also predisposes to the subluxation, as does any destructive osteomyelitis, or rather arthritis. The lesion is rather rare, and occasions persistent backache. The machine here is damaged, out of gear. The joints in the vicinity are strained and sprained when they are used, especially if they are exposed to hard usage. In rare instances the fourth lumbar vertebra slips forward on the fifth.

The only rational treatment for spondylolisthesis is rest. A light steel brace may be worn by the patient as a palliative measure, especially by older persons, but the only curative treatment is to cause by operation a bony ankylosis between the sacrum and the fifth lumbar vertebra. The pain is caused by motion in the distorted joints. It ceases when motion ceases. The actual forward displacement of one bone on the other cannot be corrected, and is of no moment. I speak, of course, of the moderately severe cases showing no damage to the cord, such as are found in patients complaining only of backache. The operation will

tax one's ingenuity if the posterior wall of the proximal part of the sacral canal is lacking.

*Kissing Spines.*—Normally between the spinous processes a distinct interval exists. In certain cases this interval is diminished, and the spines may be brought into contact, or even occasionally overlap. In the roentgenograms a condensation of the bone may be detected on the margin of each spine where it is in contact with the other. A supernumerary joint is thus formed, where it does not belong, and instead of two lateral joints on which the vertebrae swing forward and backward, as on a hinge, the patient has three, arranged as a triangle. Any one or all of these may be sprained, giving a lumbago, a sciatica or both. Some specimens of spinous processes in my possession show cartilage on the margin of the spine, and that the spines are actually in contact



Fig. 1.—A, spondylolisthesis, the result of smallpox with spondylitis eight years previously. This caused severe backache and attacks of paralysis. The patient was cured by the insertion of a bone graft. B, spondylolisthesis, probably the result of typhoid thirty years previously. Note the evidence of disease in the third and fourth lumbar vertebrae and the spurring of the fifth. The patient has suffered from backache for many years, but won a heavyweight wrestling contest five years after typhoid, and still indulges in hard physical work. C, anteroposterior view of the spine shown in B. Note the bony bridge between the third and fourth lumbar vertebrae, and the irregularities in the lateral articulations.

can be demonstrated at operation. A joint in this situation is exposed to constant sprain.

This is a comparatively rare cause of backache, but, I believe, a very real one. The physical signs are not clearcut. In spite of the pain, motion, except in extension, is not usually restricted. A list of the trunk may be present. The diagnosis is made by means of the roentgenograms, and is usually missed by the roentgenographer. The possibility of the lesion should be kept in mind.



If motion in the lumbar spine is restricted by a brace, the pain will be lessened, but the only rational treatment is operative. An anklyosing operation may be done on the two vertebrae the spines of which impinge, or better yet, and far simpler, one or both spines may be amputated with a pair of Hibbs bone forceps close to their origin from the arches.

*Congenital Anomalies.*—Apparently the spine in the lumbosacral region is undergoing evolution in the human race. The fifth lumbar vertebra may actually be incorporated with the sacrum, to form a sacral segment, or the first sacral segment may form a part of the lumbar spine



Fig. 2.—Kissing spines. Note the approximation of the spine of the fourth vertebra to that of the fifth, with the squaring and condensation of their contiguous surfaces. The patient was a man of 56, who also had second type arthritis, as determined by examination of a piece of a lateral articulation obtained at a Hibbs' operation.

as a sixth lumbar vertebra. Whether or not the variation constitutes a weakness I do not know.

A change in the plane of the lateral lumbosacral articulations predisposes to spondylolisthesis, as has been noted. Sometimes these articulations are in different planes, sagittal on one side and coronal on the other. Now the machine is out of gear. It is easily injured, as any other machine would be which did not work smoothly. The joints are

strained and sprained. Backache is common, and is frequently quite severe. Strangely enough, in this case, as in the other congenital anomalies, the backache rarely makes its appearance until the third decade of life. The tissues seem to be elastic enough to adapt themselves to the condition until that period.

Variations in the size and shape of the lateral processes are frequent. They may vary in size on the two sides, without causing symptoms, but when one of them is incorporated with the first segment of the sacrum,



Fig. 3.—Low power photomicrograph of a piece of one of the spines shown in figure 2. Cartilage cells appear in the fibrous tissue close to the bone, and between them and the bone is a strip of calcified fibrous tissue.

or is so large and of such a shape as to articulate with the sacrum or with the ilium, this portion of the spine, viewed as a machine, functions badly. It is exposed to strains. Its joints are frequently sprained. They become repeatedly the seat of a traumatic arthritis. Pain is felt in the back and, as in the other lesions in this vicinity, is referred down the sciatic distribution. If the two lateral processes are enlarged symmetrically and articulate with the pelvic bones, the presence of the extra



Fig. 4.—*A*, low power photomicrograph of a piece of a spinous process removed from another patient. Note the layer of calcified fibrocartilage adjoining the bone. *B*, low power photomicrograph of a piece of a spinous process removed from another patient. Most of the field is occupied by a calcified area of necrotic tissue. In the fibrous tissue between it and the bone appear cartilage cells.

joints must predispose to injury, to traumatic arthritis. In any of these conditions one can establish with the roentgenograms a definite anatomic fact which can explain the symptoms of which the patient complains.

On the other hand, asymmetry in itself is no cause of backache, provided that the joints are not sprained. The roentgenograms show all sorts of distortions and changes in the shape of the vertebrae in scoliosis, for instance, and the patient may suffer no pain whatever. This makes one suspicious of such vague terms as "static joint diseases" (Preiser), "balance" or "posture." In this connection the reader is referred to an excellent paper by the late Robert Patek of the Stanford

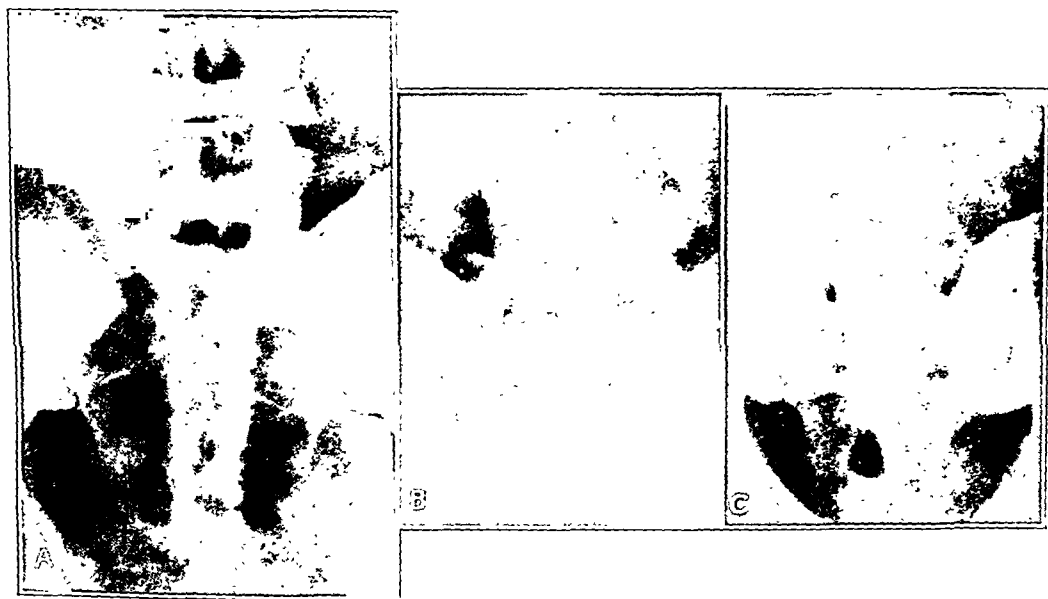


Fig. 5.—*A*, lateral articulations between the fifth lumbar vertebra and the sacrum are in different planes, sagittal on one side and coronal on the other. *B*, congenital anomaly of the fifth lumbar vertebra. Large lateral processes articulate with the sacrum, and on one side probably with the ilium. *C*, congenital anomaly of the fifth lumbar vertebra. The large lateral process on one side articulates with the sacrum.

Clinic, which has not received the attention it merits, perhaps because it contained little of theory and much of fact.<sup>1</sup>

One's chief efforts in these cases are to be directed to limiting motion in the lumbosacral region, and hence to protecting the joints from sprain. The required restraint may be furnished by a light steel brace, or an operation may be necessary. Perhaps the simplest way out is to ankylose

1. Patek, Robert: Static Deformities as a Factor in the Production of So-Called Hypertrophic Arthritis, *J. Orthop. Surg.* **19**:324, 1921.

the fifth lumbar vertebra to the sacrum. Some operators advise the amputation of a large winglike lateral process on the fifth lumbar vertebra, but the operation is difficult and bloody, and carries a heavy danger of injury to the spinal nerve roots. The other operation is easier and eminently satisfactory.

Without the same definite relation of cause and effect—and I therefore hesitate to include it here—is the backache suffered by persons who lack a proper range of dorsal flexion in their ankle joints, that is, whose

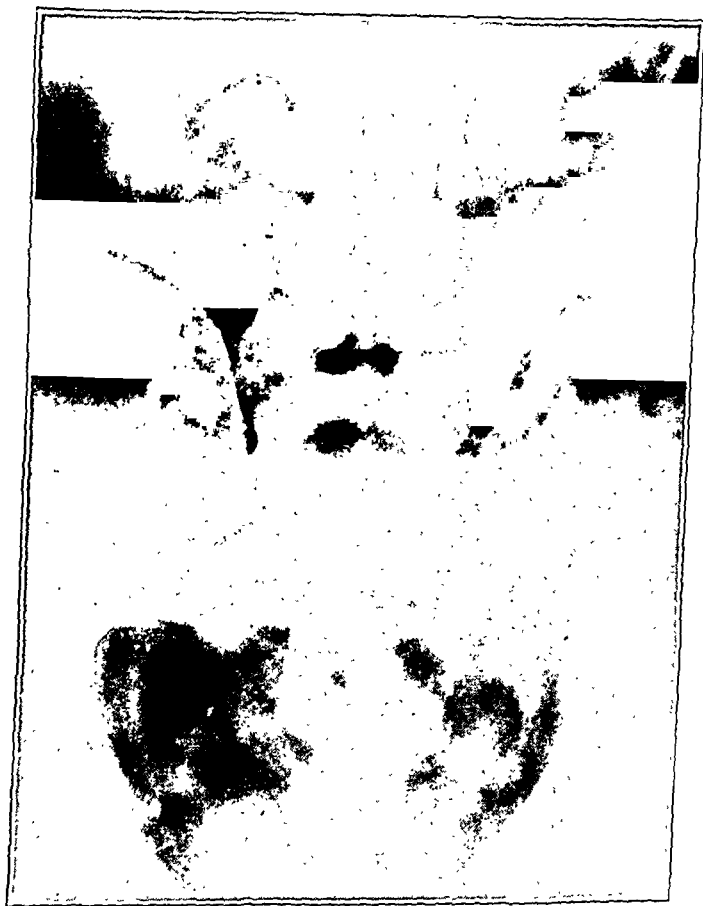


Fig. 6.—Congenital anomaly of the first sacral segment. It forms a sixth lumbar vertebra with a large lateral process on one side, articulating with the sacrum itself.

calf muscles are short. In cases of persistent backache, for which no other cause can be found, I suggest this comparatively frequent deformity be sought. In the milder cases, high heels suffice for treatment. In severe cases, the tendo calcaneus should be lengthened.

*Lesions of the Sacro-Iliac Joint.*—Infectious arthritis is a comparatively frequent cause of backache. With this backache a persistent sciatica is associated. Sensitiveness over the joint is present, and, especially in tuberculosis, sensitiveness over the anterior aspect of the

joint, with infiltration, can be detected by palpation with the finger in the rectum. With this disease the patient will limp, and his trunk in standing will exhibit a lurch away from the affected side. The lumbar muscles show the characteristic spasm, and motion in the lumbar spine, especially flexion, is decidedly limited. The roentgenograms confirm the diagnosis. The only known satisfactory treatment of sacro-iliac tuberculosis is operative ankylosis. With any other treatment the outcome is practically invariably fatal.

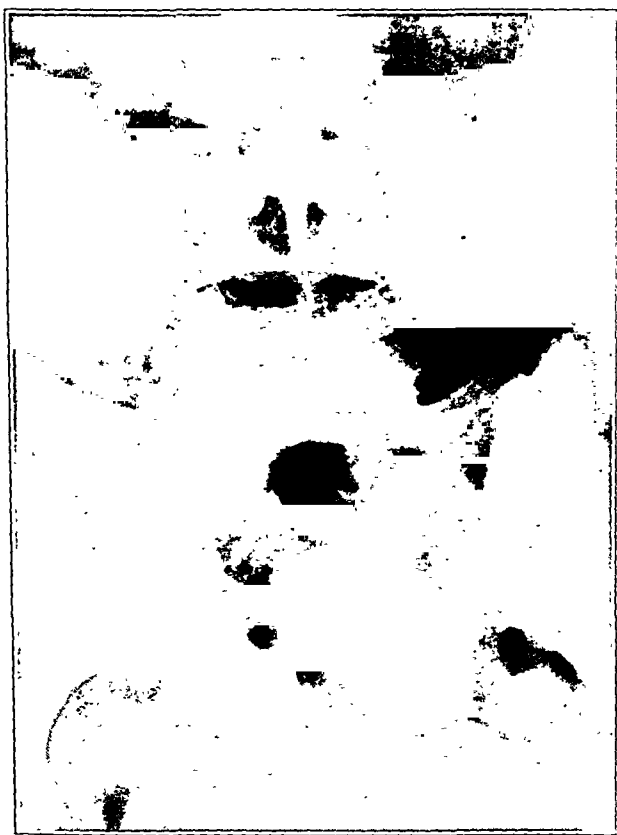


Fig. 7.—Tuberculosis of the sacro-iliac joint.

*Sacro-Iliac Displacement.*—Under this and various other names—sacro-iliac slip, sacro-iliac sprain, sacro-iliac subluxation, pubic subluxation, rotation of the innominate bone—a lesion has been described which has occasioned a great amount of controversy. The existence of any such lesion has been disputed. A glance into the past may help one to understand the matter.

Older physicians will recall the standard treatment for sciatica. It consisted in “stretching the sciatic nerve.” This was supposed to free it from inflammatory adhesions. Under narcosis the thigh on the

affected side of the supine patient was flexed to a right angle, and then the leg was forcibly extended, the so-called Kernig manipulation. Sometimes the flexion of the entire extremity was carried to such an extent that the foot approached the patient's face. Paralysis of the sciatic nerve has been caused in this way. This was the so-called dry stretching. If the manipulation were not successful, bloody stretching was done at a later time. The sciatic nerve was exposed in the back of the thigh, and the delicate connections of the nerve with the tissues in which it lay were identified as adhesions. The operator then hooked his first and second fingers under the nerve, separated the "adhesions" throughout the extent of its exposed portion and then stretched the nerve by almost lifting the patient from the table. In spite of the absurd theory on which these operations were done, the fact that they often were successful appeared to justify it.



Fig. 8.—*A*, pubic subluxation; rotation of the innominate bone. This picture was taken with the patient prone. It shows the pubes slightly higher on the right. *B*, this picture of the same patient, standing with her weight on the right foot, shows how the displacement is increased. *C*, in this picture the patient stands on her left foot, and the displacement disappears. *A*, *B* and *C* present the classic pictures of this lesion. When the rotation has been corrected by manipulation, these displacements are not obtained.

About twenty-five years ago a reformed osteopath, studying medicine at Harvard Medical School, interested the orthopedic staff in the subject of slip of the sacro-iliac joint as a cause of lumbago and sciatica, and precipitated a controversy which has endured to the present. The treatment recommended was essentially the same as that for stretching the sciatic nerve, except that for bloody stretching was substituted simple forced superextension of the thigh on the body.

A fairly definite symptomatology was built up for the lesion. As a rule, the onset was sudden. The patient, while lifting or straining, felt a sudden pain in the region of the sacro-iliac joint, which often ran

down the sciatic distribution. This often completely incapacitated him. All motions in the lower part of the spine were impossible, the lumbar muscles were in spasm and the trunk was drawn over to the side. The Kernig sign was strongly positive. Sensitiveness of the sacro-iliac joint to deep pressure was present, but the patient did not limp.

The treatment outlined usually was successful, when care had been used in the diagnosis. Often during the manipulation a slight click could be felt, or even be distinctly heard by bystanders. However, the fact that no displacement could ever be detected by roentgenograms cast doubt on the correctness of the diagnosis. About ten years ago Dr. H. R. Allen of Indianapolis advanced the idea that the displacement of the sacro-iliac joint was not up or down, but was simply a fixed rotation of the ilium on the sacrum, and that the place to look for its manifestation was not at this joint but at the symphysis pubis. As Dr. Allen expressed it tersely, if one wanted to tell the time, one would not look at the center arbor of the time piece around which the hands move, but out at the ends of the hands. This was done, the fixed displacement was identified at the symphysis pubis and for many the problem was solved. Unfortunately, the idea does not seem to have attracted much attention. It explains well how treatment hitherto carried out on an erroneous theory was nevertheless successful.

The displacement of the pubes is usually upward on the affected side. If, then, the usual first maneuver of replacement is tried—the forced Kernig maneuver, dry stretching of the sciatic nerve—the hamstring muscles, attached to the tibia and to the ischial tuberosity, will pull the os innominatum in such a way as to increase the displacement. “Dry stretching” of the sciatic nerve will not cure the condition. If the patient is turned on his face, and if his thigh is then superextended, by simple manipulation, or after incision and “freeing of sciatic adhesions,” the Y ligament will pull the pubes downward and reduce the displacement.

Occasionally the displacement of the pubes is downward, on the affected side. Then the forced Kernig manipulation will reduce it.

Here then is a set of symptoms and clinical signs perfectly compatible with a diagnosis of a sprain of the sacro-iliac joint. Roentgenograms of the symphysis pubis show an anatomic condition capable of explaining the sacro-iliac sprain. When the displacement of the pubes is corrected, as shown roentgenologically, the symptoms and physical signs disappear, leaving perhaps only a slight feeling of soreness. If the clinical picture presents itself again, the procedure can be repeated. It should not be necessary to add that the simple manipulation here described would not cure an inflammation of the sciatic nerve, a fibrositis, a myositis, a fasciitis, a radiculitis or the results of pressure on a spinal nerve.



*Neoplasms.*—Malignant bony growths can cause an agonizing backache, for which nothing but narcotics can be prescribed. Their presence should always be suspected, particularly in persons suffering from malignant growths elsewhere.

#### CONCLUSION

I have detailed lesions of the motor apparatus which can be established as a reasonable cause for the backaches seen in the clinic and in private practice. In the treatment of this symptom one should rely on facts rather than on theories. In diseases and injuries of bones and joints one must adopt the methods of modern medicine. One must discount the extravagant claims of cure made by the advocate of some peculiar means of treatment, and must demand some concrete evidence of the truth of his claims. Here as elsewhere in medicine one's ideas must be based on the correlation of sound pathologic observation, clinical evidence and experiment.

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# BONE AND CALCULI IN THE COLLECTING TUBULES OF THE KIDNEY

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CHICAGO

In this paper the occurrence of bone in the human kidney in close association with parenchymatous stones will be described and its bearing on the theory of osteogenesis pointed out.

The occurrence of bone in the kidney under experimental conditions has attracted much study since the original demonstration by Sacerdotti and Frattin<sup>1</sup> (1901). It had long been demonstrated that following ligation of the renal artery or artery and veins, there occurs a massive necrosis of the renal substance, but not of the renal pelvis and ureter because of a different vascular supply. Extensive calcification of the necrotic renal tissue occurs within a few days (Blessig<sup>2</sup>), and bone<sup>3</sup> develops some weeks later, forming chiefly and constantly beneath the mucosa of the pelvis with spurs extending into the remains of the kidney. The demonstration<sup>3</sup> of a bone-stimulating effect of the epithelium of the renal pelvis makes it probable that this was the cause of the bone formation in the experiments of Sacerdotti-Frattin, especially since it does not occur if the epithelium of the pelvis dies, for example, as a result of ligation of the ureter and the renal artery simultaneously.

Bone formation in the kidney in man associated with renal calculi was first demonstrated by Phemister,<sup>4</sup> who observed it in three instances in two patients. In each instance living spongy bone with fibrous and fatty marrow occurred in a pedunculated mass of fibrous tissue attached to the renal pelvis and partly surrounded by stone. The inorganic portion of the stone was mainly calcium oxalate, with lesser amounts of calcium carbonate and phosphate. A similar kind of bone asso-

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1. Sacerdotti, C., and Frattin, G.: Ueber die heteroplastische Knochenbildung, *Arch. f. path. Anat.* **168**:431, 1902.

2. Blessig: Ueber die Veränderungen der Niere nach Unterbindung der Nieren Arterie, *Virchows Arch. f. path. Anat.* **16**:120, 1859.

3. Huggins, C. B.: Influence of Urinary Tract Mucosa on the Experimental Production of Bone, *Proc. Soc. Exper. Biol. & Med.* **27**:349, 1930; The Formation of Bone Under the Influence of Epithelium of the Urinary Tract, *Arch. Surg.* **22**:377 (March) 1931; Transplantation of Ureteral Segments to the Abdominal Wall, *Proc. Soc. Exper. Biol. & Med.* **28**:125, 1930.

4. Phemister, D. B.: Ossification in Kidney Stones Attached to the Renal Pelvis, *Ann. Surg.* **78**:239, 1923.

ciated with renal calculi occurring in pedunculated masses in the renal pelvis and in part beneath the epithelium of the pelvis has recently been described by Hellström.<sup>5</sup>

Partial replacement by bone of calcified areas in tuberculosis of the kidney, hypernephroma<sup>4</sup> and dermoid cysts of the kidney<sup>6</sup> has been observed.

A different type of bone formation in the human kidney, comparable to the Sacerdotti-Frattin experiment, was recently described by Schmorl.<sup>7</sup> Complete infarction of the blood supply of the kidney occurred with subsequent formation of bone beneath the mucosa of the pelvis. This is the only example of its kind in the literature.

Bone occurring under still different conditions was recently observed in the histologic examination of two human kidneys extirpated because of renal calculous disease. In the first case the bone was of a size easily visible to the unaided eye; in the second, it was of microscopic dimensions.

#### CASE REPORTS

**CASE 1.—History.**—A man, aged 41, entered the University of Chicago Clinics complaining of left lumbar colic radiating to the groin, of four years' duration. Pus had been present in the urine for at least a year, and a stone had been passed on five occasions. Roentgenograms of the region of the kidney demonstrated rapid growth in the size of the stone in the last six months. Slight pain in the loin was elicited on palpation. The urine contained a moderate number of leukocytes and erythrocytes, found on cystoscopy to be coming entirely from the left kidney. The left kidney was found infected with *Staphylococcus aureus*. Left nephrectomy was done. Roentgenograms of the excised kidney before and after injection of sodium iodide showed in the lower pole in addition to other shadows a crenated shadow of the density of calcium (figs. 1 and 2) which was the bone described in detail under gross pathologic examination.

**Gross Pathologic Examination.**—The kidney was symmetrically enlarged and weighed 190 Gm. The capsule stripped readily. The pelvis contained 30 cc. of purulent urine, two large and many small calculi. In the lower pole of the kidney was a calcified mass about 0.5 by 0.5 by 0.3 cm. situated in one of the renal papillae and densely adherent to its surroundings. This was excised in situ, fixed in formaldehyde, placed in 5 per cent nitric acid for seven days, and sectioned in paraffin.

**Microscopic Examination.**—This last mentioned calcified area was composed chiefly of spongy bone, and to a much less extent of stone. It was situated in the parenchyma of the kidney in one of the collecting tubules; most of the epithelium lining the tubule had disappeared, but in several areas the cuboidal epithelial lining had been well preserved and served to identify the tubule. There was a cleft (fig. 3) separating the calcified mass from the wall of the tubule and the renal medulla, in places interrupted by fibrovascular invasions entering the bone, carrying

5. Hellström, J.: Ein Fall von metaplastischer Knochenbildung in der Niere in Zusammenhang mit Nierenstein, *Ztschr. f. Urol.* **25**:401, 1931.

6. Pick, Ludwig: Personal communication.

7. Schmorl, G.: *Verhandl. d. deutsch. path. Gesellsch.* **25**:190, 1930.

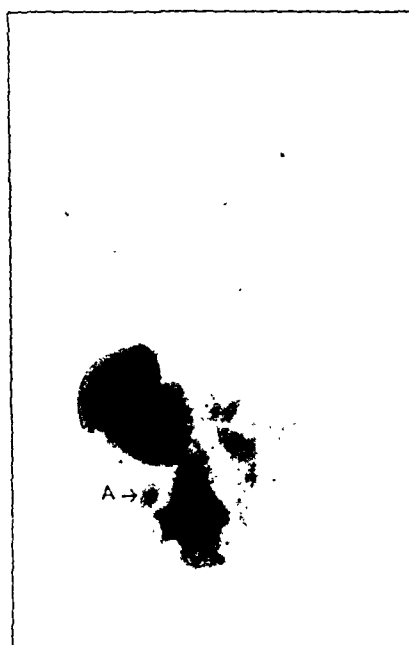


Fig. 1 (case 1).—Roentgenogram of excised kidney containing many calculi and bone. The bone is the crenated shadow (*A*).

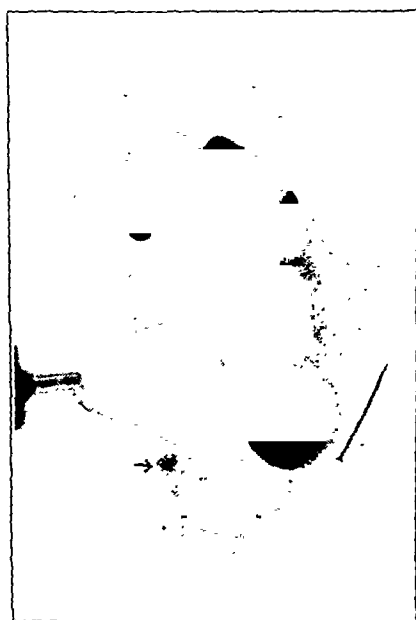


Fig. 2 (case 1).—Renal pelvis injected with sodium iodide. The bone is opposite the arrow.

its blood supply. The bone was cancellous in structure, containing fibrous and fatty marrow. The bone lacunae were filled for the most part with typical living bone cells with easily demonstrable canaliculi (fig. 4).

An interesting relationship existed between the bone and the calculous material. In each of the sections containing bone, the matrix of the inorganic calculus might be seen, but more in the juxtapelvic than in the deeper lying areas of the bone. In the former areas, the margin of the bone was nearly surrounded by the



Fig. 3 (case 1).—Photomicrograph showing approximately two thirds of the extent of the bone in the kidney;  $\times 25$ . Note cleft (*c*) between the calcified mass and the parenchyma.

concentrically laminated, escalloped stone which near the periphery contained a continuous band of a heavily pigmented, brown amorphous material differing widely from the rest of the stone (fig. 5). The stone was easily recognized and presented a concentrically ringed, acellular form, staining deeply blue with hematoxylin. The concentric laminations of the stone were visible only at the periphery of the bone. The center of the bone was occupied in part by crystalline and amorphous

stone material, presenting irregularly curved and angled spaces. In places this material had disappeared, leaving only empty clefts of bizarre shape, mostly with acute angles (fig. 5).

In many places the laminated, acellular stone merged with the living bone in an unmistakable manner, and the bone seemed to have been molded in the form previously occupied by the stone (fig. 6). There was thus no distinct boundary between the bone and the stone in these locations.



Fig. 4 (case 1).—Photomicrograph showing the bone lacunae and canaliculi;  $\times 325$ .

Otherwise, sections taken through the renal substance in several places showed essentially normal appearing glomeruli, a few of which were undergoing calcification. There were numerous areas of lymphocytic infiltration throughout the parenchyma of the kidney. In several locations in the pyramids calcareous, concentrically laminated calculi might be seen in dilated tubules of the renal papillae (fig. 5 C).

**CASE 2.—History.**—A woman, aged 30, entered the University of Chicago Clinics complaining of a constant sharp pain in the left loin, of one week's duration. Previously well, she developed six weeks before a mild acute respiratory infection accompanied by vague abdominal discomfort and constipation lasting the greater part of five weeks; recently left renal colic developed. There were no urinary symptoms. Examination disclosed tenderness in the region of the left kidney. The urine at first examination was normal; later it contained many polymorphonuclear



Fig. 5 (case 1).—The margin of the stone, showing the escalloped edge, heavily pigmented brown band (*A*) and bone (*B*), and containing irregularly shaped clefts;  $\times 80$ . A microlith is seen at *C*.

leukocytes. Roentgen examination showed many diffuse radiopaque spots in the region of the left kidney with a shadow of a ureteral stone opposite the spine of second lumbar vertebra. Cystoscopy demonstrated lack of function from the left kidney and an impassable obstruction in the upper ureter. Exploration of the kidney showed an impacted stone in the upper ureter, but no free stones in the

renal pelvis; the renal papillae were loaded with small calculi. Complete removal of all the calculi was impossible except by nephrectomy, which was done.

*Gross Pathologic Examination.*—The kidney was moderately enlarged and edematous and weighed 240 Gm. The fibrous capsule stripped easily. A stone was found impacted 1 cm. below the ureteropelvic junction. The renal pelvis was lined with a hemorrhagic, swollen mucosa, and contained no stones. In each of



Fig. 6 (case 1).—An area where direct union may be seen between the laminated stone (*S*) and bone (*B*);  $\times 85$ . This direct invasive replacement of the stone by bone was seen in many areas in the sections.

the papillary regions of the renal pyramids, a collection of small, hard, black stones, some as large as 0.5 cm. in diameter was found. These areas were excised for microscopic examination. Chemical analysis of one of the stones showed: nitrogen, 1.1 per cent; tertiary calcium phosphate, 10.4 per cent; calcium as oxalate, 75.8 per cent; unaccounted for, 12.7 per cent. Culture from the renal pelvis was sterile.





Fig. 7 (case 2).—Longitudinal section through pyramid showing calculi in collecting tubules;  $\times 10$ .



Fig. 8 (case 2).—Photomicrograph showing microliths in the renal papillae, one of which is presenting at the mouth of the tubule;  $\times 50$ .

*Microscopic Examination.*—Moderate edema of the renal parenchyma was seen with slight extravasation of blood and collections of leukocytes, especially beneath the pelvic mucosa. There was a protein exudate in many of the tubules and moderate dilatation of some of the convoluted tubules.

The chief interest centered in the papillae, where most of the collecting tubules were dilated, some tremendously, with thinning of the epithelium in places. Many of these tubules were filled with calculi (figs. 7 and 8), which were concentrically

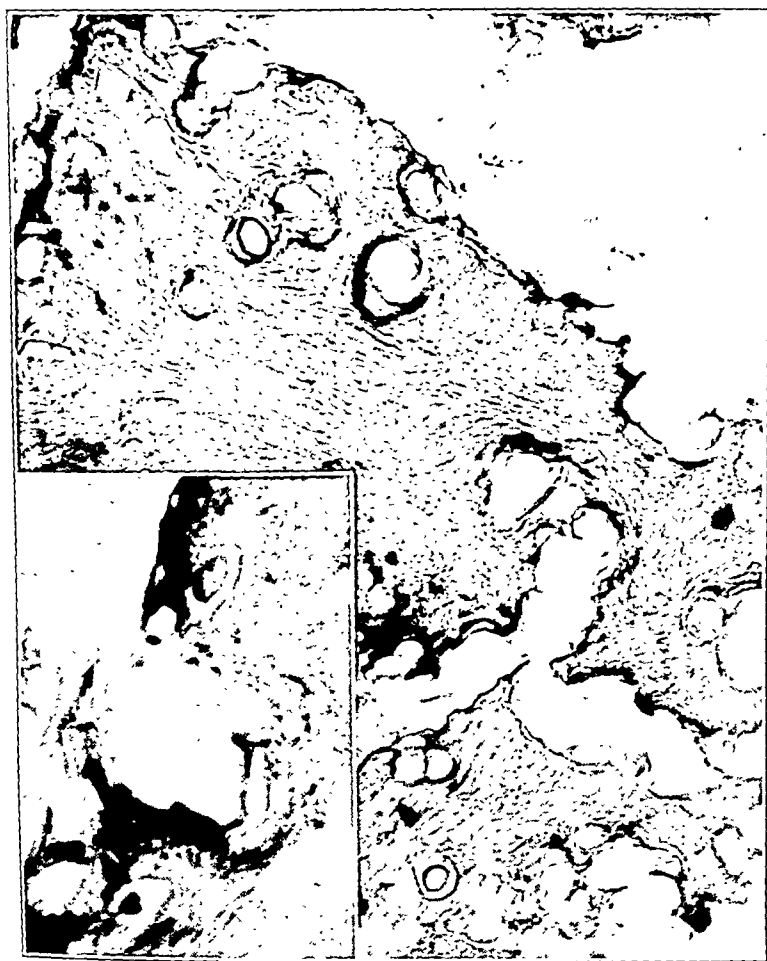


Fig. 9 (case 2).—Photomicrograph showing the fibrous nature of the matrix and the bone lacunae, some of which are empty;  $\times 1,500$ . The insert shows detail of the bone cells.

laminated, took hematoxylin well, and had a granular, amorphous nucleus. Several of these calculi were adherent to the tubular wall, and in one location a calculus was being invaded by connective tissue.

In one set of more than twelve consecutive secretions of these stone-bearing papillae, there was seen a calculus the concentrically layered periphery of which nearly surrounded a homogeneous pink-staining mass of bone. The bone was

attached at one point to the parenchyma of the kidney, and fibrous tissue might be seen entering it. Many of the lacunae were empty, but some contained typical bone cells. The matrix was seen under higher magnification to be fibrous (fig. 9). No direct continuation with the stone as in case 1 could be seen.

#### MICROLITHS IN THE KIDNEY TUBULES

As mentioned, small concentrically laminated calculi were found in the lumen of the renal-collecting tubules in these two cases so that a brief consideration of this phenomenon is germane to the present



Fig. 10.—A typical laminated microlith from the collecting tubule of a kidney excised because of a coral calculus;  $\times 100$ . The cuboidal epithelium of the tubule may be seen opposite the arrows.

discussion. These calculi have occasionally been found in the tubules of the human kidney as well as in lower animals. They are distinguished from all other calcium deposits in the kidney by their lamellar arrangement and by their free position in the tubule. They have varied in our experience from purely microscopic dimensions to a size of 1 by 0.5 by 0.5 cm., and doubtless at times are larger. They must be differentiated from calcium infarcts occurring outside the tubules in the

pyramids and the closely related structures described by Lichtenstern,<sup>8</sup> who described calcified deposits attached to the renal parenchyma projecting into the lumen of the tubules. The relation of these small calculi to calcified cylindroids<sup>9</sup> is unknown but may be close.

These microliths have been observed in many of the cases in which kidney stones have been experimentally produced. These include calculi forming (1) after the feeding of the oxamide;<sup>10</sup> (2) after intravenous injections of uric acid and some of its constituents;<sup>11</sup> (3) after intravenous oxalates,<sup>12</sup> and (4) in vitamin A deficiency.<sup>13</sup>

In the adult, renal microlithiasis has been mentioned by Braasch<sup>14</sup> and briefly described by Crabtree.<sup>15</sup> Microliths composed of laminated deposits of uric acid, the uric acid infarcts, are frequently seen in the collecting tubules of infants dying in the first weeks of life, and are known to every pathologist.

In this laboratory, laminated calculi in the tubules in adults have been found in four of sixteen kidneys excised for calculous disease. It has been our experience that unless serial sections of the renal pyramids are made they are easily overlooked; they have not been found where there has been much necrosis of the papillae from the pressure of a coexisting hydronephrosis or from infection. They have been found only in the collecting tubules. It is our feeling that these surgically inaccessible bodies may be a source of recurrence of calculi after conservative operation.

There is also evidence that these structures are closely related to the development of grosser calculi found in the renal pelvis. The evidence may be summarized thus: (1) clinical cases such as case 2, in which one of the calculi obviously passed out of the renal papilla and caused complete ureteral obstruction; (2) the fact that these microliths have the same nucleus formation and concentrically lamellar arrangement as the gross calculi and must adsorb or cause precipitation of similar

8. Lichtenstern, R.: Mikrolithiasis, *Wien. klin. Wchnschr.* **39**:1156, 1926.

9. Lubarsch, O., in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, vol. 6, p. 564.

10. Ebstein, W., and Nicolaier, A.: Ueber die experimentelle Erzeugung der Harnsteinen, Wiesbaden, J. F. Bergmann, 1891.

11. Heidenhain: *Arch. f. d. ges. Physiol.* **9**:23, 1874. Ebstein, W., and Nicolaier, A.: *Virchows Arch. f. path. Anat.* **143**:337, 1896. Minkowski, O.: *Arch. f. exper. Path. u. Pharmacol.* **41**:375, 1898.

12. Ebstein, W., and Nicolaier, A.: Ueber die Wirkung der Oxalsäure und einiger ihrer Derivate auf die Nieren, *Virchows Arch. f. path. Anat.* **148**:366, 1897. Keyser, L. D.: The Mechanism of the Formation of Urinary Calculi, *Ann. Surg.* **77**:210, 1923.

13. Van Leersum, E. C.: Vitamin A Deficiency and Urolithiasis, *J. Biol. Chem.* **76**:137, 1928.

14. Braasch, W. F.: Unusual Types of Urinary Lithiasis, *J. Urol.* **23**:1, 1930.

15. Crabtree, E. C.: *Tr. Am. A. Gen.-Urin. Surgeons* **23**:17, 1930.

isomorphic crystals in a highly saturated solution of the difficultly soluble salts of which they are composed; (3) frequent occurrence of the microliths in experimental lithiasis, and (4) two experiments which may be recounted briefly.

EXPERIMENT 1.—Three groups of three albino rats were fed oxamide by mouth in quantities of from 1 to 3 Gm. daily for one, two and three days, and then killed. In two of three rats killed at forty-eight hours, no gross stones were found in the urinary tract, but crystalline deposits were found in the collecting tubules on histologic examination. In the rats killed at three days, gross calculi were found accompanied by crystalline deposits and microliths in the collecting tubules.

EXPERIMENT 2.—Oxamide was fed by mouth to five albino rats in approximately 1 Gm. amounts daily for seventeen days and then discontinued. The animals were sectioned thirty-three days later. One rat had bilateral pelvic calculi and another had a stone impacted in a ureter. In three rats no calculi were found, and sections of the kidney showed no parenchymatous microliths. In four rats similarly treated and killed at seventeen days as controls, there were massive deposits of oxamide in the collecting tubules as well as elsewhere in the urinary tract.

These simple experiments show, first, that the deposition of concentrically laminated formations of oxamide is the first evidence of the formation of calculi composed of oxamide in the rat; and secondly, that unless the action of the stone-forming agent persists, these bodies are liable to be discharged from the collecting tubules, so that examination at a later date would give no clue to the fact that there had originally been calculi in the renal tubules.

#### COMMENT

In the previously reported cases of ossification in the human kidney, the bone was found in close association with the pelvis, whereas here the bone was in the parenchyma of the kidney. The origin of the bone is of interest from a theoretical standpoint. Search was made for areas of mucosa of the renal pelvis in this area, but none was found in close association with the bone, so that it was necessary to discard the idea that the bone arose as a result of an epithelial stimulus.

The bone in each case was in immediate proximity to stone formation, and there were many locations where direct union occurred between the bone and stone (fig. 6). This is considered strong evidence that the bone formed in a somewhat similar way to the histologic picture<sup>16</sup> of creeping substitution in which there is invasive replacement of aseptic dead bone by new living bone. The point of greatest theoretical interest is that in the present cases the process is a creeping

16. Axhausen, G.: Knochennekrose und Sequesterbildung, *Deutsche med. Wchnschr.* 40:1 and 111, 1914. Phemister, D. B.: Repair of Bone in the Presence of Aseptic Necrosis, *J. Bone & Joint Surg.* 12:769, 1930.

substitution of stone by bone. This is considered good evidence that accumulation of difficultly soluble calcium salts can provide a stimulus for bone formation in certain connective tissue.

As Phemister and Hellström emphasize, it is probable that bone formation in kidneys containing calculi occurs more frequently than the literature indicates.

#### SUMMARY

1. A type of bone formation in the human kidney located in the medulla in association with calculi in the collecting tubules is described.
2. It is most probable that the calculi served as the stimulus for bone formation. Creeping substitution of stone by the bone is demonstrated.
3. The presence and significance of these intratubular calculi are discussed.

# RELATION OF TRAUMA TO RUPTURE OF HOLLOW ABDOMINAL VISCERA

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Many patients who suffer from various diseases of the intra-abdominal organs attribute the onset of their trouble to a strain or other abdominal injury. Frequently in such cases the attending physician agrees with the theory of traumatic etiology. The result is, when the circumstances permit, a claim for damages or compensation. There is hardly a disease of the abdominal viscera that has not been the subject of personal injury litigation. The claim of traumatic rupture of gastric or duodenal ulcers is a common example. Claims have been made in cases of this kind in which either an alleged or a real injury has preceded the rupture by from a few hours to several days.

Several cases of this kind have come under my observation, and I have always felt that the laws of hydromechanics apply to the abdomen and its fluid contents. However, there is no proof that the laws of fluid pressure in living elastic cavities are the same as those determined for rigid, nonliving containers. Moreover, I could find no reference to the behavior of fluid pressure when the containers were subdivided by one or more elastic-walled compartments.

In an attempt to answer these questions I have made a series of observations in order to determine whether or not the law of hydrostatics of Pascal applies to the living abdominal cavity with its fluid-containing hollow viscera, and also to determine the pressure relations in the abdominal cavity in those cases in which a true traumatic rupture of a viscus did occur.

Pascal's law is as follows: "Pressure applied from without to an enclosed fluid (liquids and gases) is transmitted equally in all directions without loss, and acts with equal force on all surfaces." This law applies to fluids within a single enclosure. No information could be found regarding the application of this law in enclosures subdivided into compartments by elastic membranes. To determine the pressure relations in such a system of fluid containers was the object of this study.

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In order to visualize more clearly the changes that took place in the interposing membranes during changes in pressure, experiments were made with apparatus consisting of glass and rubber before experiments were made on living dogs.

# EXPERIMENTS

EXPERIMENT 1.—A hole was made in the side of a florence flask by means of a blow torch. This hole was enlarged by heat, and a flange was formed about its edge. Over this opening in the flask a sheet of rubber tissue was fastened so that it was air-tight and water-tight (fig. 1 *a, B*). The mouth of the flask was closed by a rubber stopper containing two perforations through which glass tubes were inserted. One tube that entered the flask remained open. The second tube was attached to a rubber finger cot by a water-tight connection (fig. 1 *a, A*). The external ends of the tubes connected with U-shaped mercury manometers. The

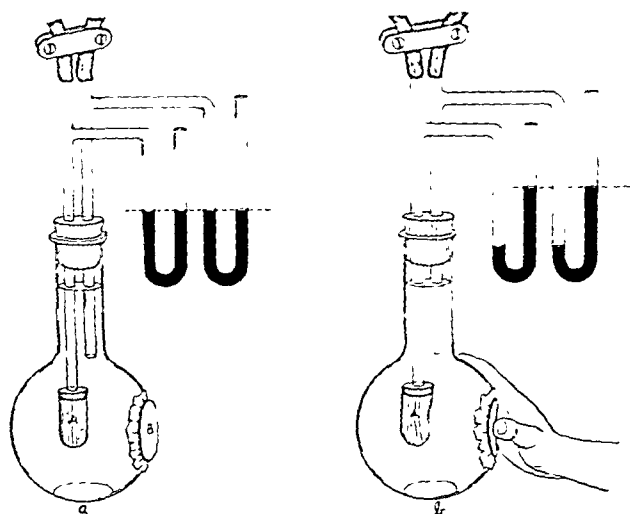


Fig. 1.—Diagrammatic representation of experiment 1.

sac (*A*) was filled with water and the flask was filled with water nearly to the top. In the assembling of the apparatus by insertion of the stopper into the neck of the flask there was some compression of fluid in the system, and the mercury rose in both manometers to an equal degree. In order to start the observations with the enclosed fluids at atmospheric pressure, a T-tube was interposed between the flask and the manometers. To this was attached a short rubber tube that could be opened or closed by a metal clamp. The completed apparatus is shown in figure 1 *a*. It can be assumed that the body of the flask represents the abdominal cavity. The rubber diaphragm (*B*) represents an elastic flexible portion of the abdominal wall. The finger cot (*A*) represents the stomach or any intra-abdominal hollow organ.

*Observation 1.*—Pressure on the rubber diaphragm (*B*) caused the mercury to rise to an absolutely equal degree in both manometers (fig. 1 *b*). A slight pressure caused a slight rise, and a greater pressure, a greater rise, but the rise was always equal. The equal rise in both manometers, however, was not in direct proportion to the degree of pressure on the diaphragm (*B*). The reason for this is that it



takes a certain amount of pressure to overcome the elasticity of the rubber diaphragm, and this pressure was deducted from the pressure exerted on the enclosed fluids.<sup>1</sup>

As all degrees of pressure on the diaphragm (*B*) caused an equal rise in both manometers, it was demonstrated that pressure on the outer surface of the sac (*A*) was equal to the pressure on its inner surface, and it was also demonstrated that the law of Pascal holds good in a closed system with an intervening elastic membrane.

*Observation 2.*—Pressure on the diaphragm (*B*) caused a dimpling in the wall of the sac (*A*) due to a displacement of fluids in both the flask and the sac.

*Observation 3.*—Tests were made with the apparatus containing air alone, with the apparatus completely filled with water, and with various proportions of air and water both in the flask and in the sac (*A*). In all combinations of air and water, pressure on the diaphragm (*B*) caused an equal degree of pressure in both manometers.

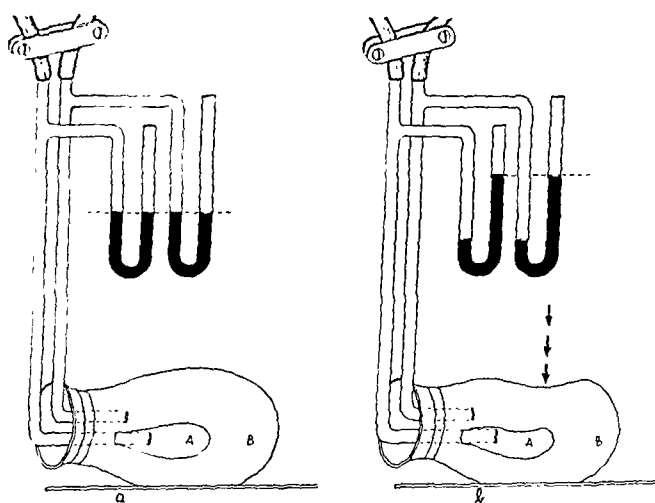


Fig. 2.—Diagrammatic representation of experiment 2.

*Observation 4.*—The rubber sac (*A*) was replaced by a 2 foot (60.9 cm.) piece of Penrose rubber tubing which was closed at its distal end. This lay coiled on the bottom of the flask, or the coils floated on the enclosed water, depending on the proportion of air and water in the two cavities of the system. All air, all water and various proportions of the two were tested, and in all instances pressure on the diaphragm (*B*) caused an equal rise in both manometers.

*Observation 5.*—Pressure on the diaphragm (*B*) caused no visible movements on the rubber tube replacing (*A*). It was known that with pressure on the diaphragm (*B*) there was a displacement of fluids as shown by the dimpling of the sac (*A*) in figure 1 *b*, but in the case of the long rubber tube this displacement of fluid occurred in a much larger volume of fluid, so that any dimpling or shrinking in the size of the tube was imperceptible.

1. This fact was determined by means of a similar apparatus, but with the rubber diaphragm in a horizontal position so that the pressure could be applied by means of graduated weights.

EXPERIMENT 2.—In this experiment the glass flask was replaced by a rubber bag in order that the conditions in the abdomen might more nearly be approached. In figure 2*a* a rubber hot water bottle (*B*) represents the abdomen and the rubber bag (*A*) represents the stomach or other intra-abdominal hollow viscera. The attachment of this apparatus to the mercury manometers was similar to that shown in figure 1.

Observation 6.—All air, all water and various combinations of these fluids were placed in the two compartments of the apparatus, and in every instance pressure on the bag (*B*) caused an equal rise in the mercury of both manometers, as shown in figure 2*b*. The hot water bottle being opaque, it was impossible to observe the sac (*A*), but it was felt that it must be dimpled on account of some displacement of fluids.

EXPERIMENT 3.—This experiment was made on a living dog. The operation was done under anesthesia with sodium amytal given intravenously. Through a midline incision the stomach was exposed. An incision was made in the stomach

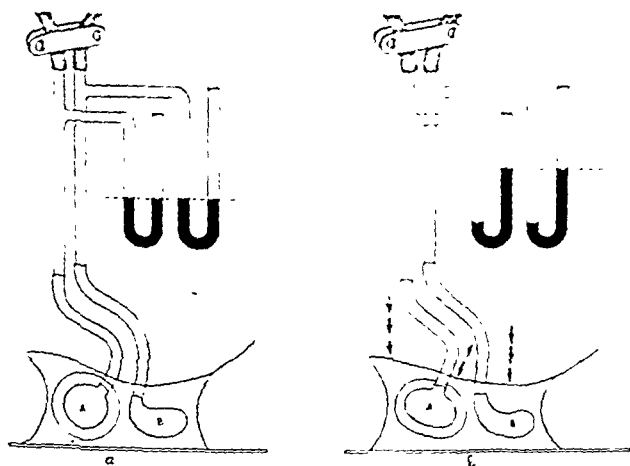


Fig. 3.—Diagrammatic representation of experiment 3.

just large enough to allow the introduction of a rubber balloon which had been filled with water without tension. The balloon was attached to a rubber tube, and about this tube the wound in the stomach wall was firmly sutured. When the stomach was opened it was found about half filled with solid and liquid food. This was not disturbed. Another rubber balloon was attached to a rubber tube and filled with water without tension. This was placed in the abdominal cavity among the loops of intestines to the right of the vertebral column. The abdominal wound was then sutured, making a firm closure about each tube at its exit. Each tube was then attached to the mercury manometers (fig. 3*a*).

Observation 7.—Pressure was applied to each region of the abdomen, and the abdomen was compressed laterally; in every instance the pressure in the two manometers was equal (fig. 3*b*).

Observation 8.—Blows on the abdomen directly over the stomach also caused an equal rise in both manometers, but no movements of the mercury could be observed that would indicate that the blow over the stomach caused a sufficient increase in the peristalsis of the stomach to lead to a rise in the intragastric pressure.

EXPERIMENT 4.—In the preceding experiment it was demonstrated that external pressure applied to the abdomen resulted in an increased intra-abdominal pressure which always equaled the intragastric pressure. In other words, any pressure on the abdomen caused an equal pressure on each side of the wall of the stomach. It would be impossible, therefore, to rupture a gastric ulcer by increasing the intra-abdominal pressure. However, if it took an appreciable amount of time for these two pressures to become equalized, an ulcer might rupture during this interval. When the movements of the columns of mercury in the manometers were observed, they appeared to rise simultaneously with the application of the pressure. However,

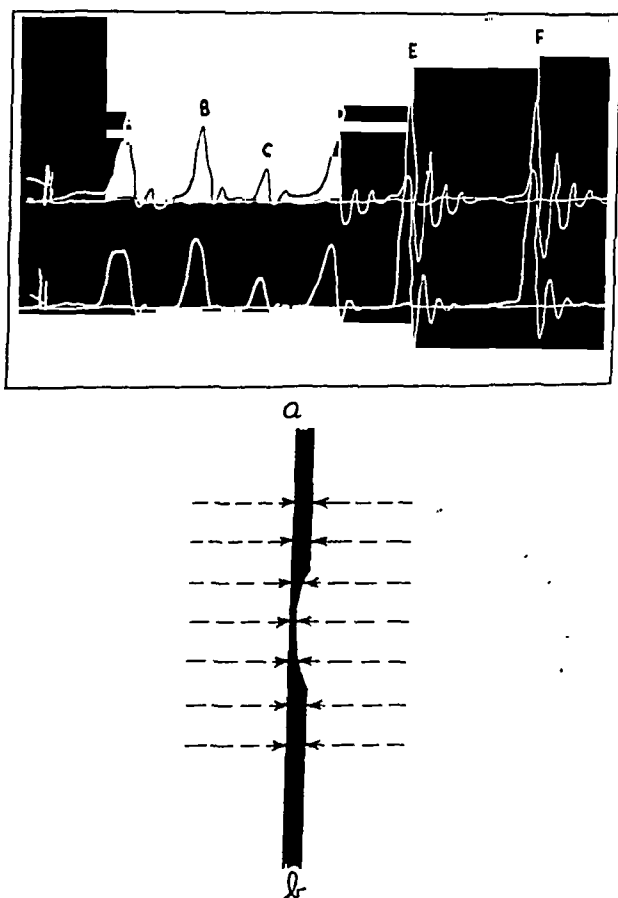


Fig. 4.—*a*, kymographic tracings in experiment 4; *b*, diagram showing equal pressure on both sides of a wall.

in order to obtain a more accurate record of the experiment, floats carrying a wire marker were inserted in the manometers. These markers, placed one directly above the other, recorded on a revolving drum the movements of the mercury.

The dog was prepared as in the preceding experiment. The anesthesia was very light, so that the dog responded to stimuli by the time the operation was completed.

*Observation 9.*—Figure 4 *a* shows the kymographic record of experiment 4. The upper curves are from the manometer attached to the stomach, while the lower curves record the pressures from the manometers attached to the balloon in the abdominal cavity. Before any pressure was applied a base line was run on the

revolving drum. This line was almost horizontal, the variations being due to the respirations.

Curves *A*, *B*, *C* and *D* resulted from various degrees of pressure on different parts of the abdomen. Curves *E* and *F* resulted from forcible blows on the abdomen with the fist. The intervening small curves are due to the elastic rebound of the rubber bags. This fact was determined by the exertion of different degrees of pressure on the rubber bags while they were outside the dog's abdomen but connected with the kymograph.

The foregoing experiments show from the kymographic record that pressure on the abdomen causing an increase in intra-abdominal pressure caused an equal and simultaneous increase in intragastric pressure.

*Observation 10.*—Forcible blows over the abdomen directly over the stomach produced no changes in the kymographic tracings that indicated additional changes in the intragastric pressure, the result of increased peristalsis.

From the foregoing observations it can be concluded that the law of Pascal applies to fluids in living elastic containers, and also that this law holds good when the container is subdivided by means of elastic partitions.

As the law of hydrostatics applies to the abdominal cavity of the dog and its contained stomach and as this law applies in a similar apparatus in vitro, it follows that it also applies to the pressure relations between the intra-abdominal cavity and all of the intra-abdominal hollow viscera. In other words, an increase in intra-abdominal pressure will cause an equal increase in the pressure in all of the hollow intra-abdominal organs, namely, the stomach, duodenum, small intestine, large intestine, appendix, gallbladder and urinary bladder, so long as their natural orifices remain closed. Therefore, it can be concluded that the wall of no hollow viscus can be ruptured by a simple increase in the intra-abdominal pressure, because the pressure on the visceral wall will be exactly equal on both sides (fig. 4 *b*).

From clinical experience, however, it is known that the hollow viscera do rupture under certain circumstances. With the exclusion of penetrating wounds, the causes of such ruptures may be grouped under three headings:

1. Diseases resulting in disintegration of the visceral wall. Common examples are the following: gangrene of the appendix, gangrene of a loop of bowel, a malignant growth on the wall of a viscus and progressive necrosis and ulcerations, such as gastric and duodenal ulcers, tuberculous ulceration of the bowel and ulceration secondary to calculi. In all of these conditions the rupture may be entirely spontaneous owing to the gradual dissolution of tissue; it may be aggravated by peristaltic waves in the adjacent visceral wall, or it may be hastened by the changes in pressure to be named later.

2. A hollow viscus may be ruptured by overinflation or over-distention. Such a condition is seldom seen unless the ruptured viscus is weakened by disease, as mentioned under group 1. In such a case the diseased viscus ruptures from overfilling and from overdistention with gases, the result of fermentation and putrefaction. A striking example of rupture from overinflation of a normal viscus is the rupture of the rectum or the large intestine following the so-called practical joke of placing the nozzle of a compressed air hose against the victim's anus.

3. Rupture of a hollow viscus may occur following external violence to the abdomen, such as severe blows or compression. The most com-

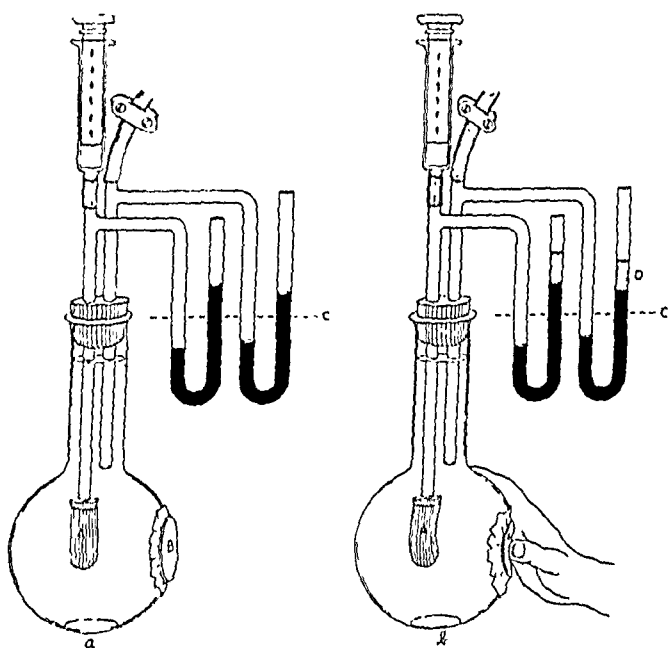


Fig. 5.—Diagrammatic representation of experiment 5.

mon example is the compression of the abdomen by the wheel of a vehicle.

In order to study the changes in intra-abdominal pressure in relation to the rupture of the hollow viscera, the following observations were made.

The first question to consider was the following: How would Pascal's law apply when one compartment in the system was raised to a higher pressure than that in the remainder of the system? It has been shown that the intra-abdominal and the intragastric pressure remain equal under ordinary conditions, but what would happen if there was an increase in the intra-abdominal pressure while the stomach was already distended with gas under pressure?

EXPERIMENT 5.—The same apparatus as shown in figure 1 was used, and a glass syringe was attached to the tube leading to the rubber sac (*A*). The mercury was allowed to settle to the same level in each manometer. The system was then closed, and by means of the syringe air was forced into the rubber sac (*A*) until it was distended under pressure.

*Observation 11.*—With the sac (*A*) distended the mercury rose in each manometer, but it rose higher in the manometer connecting with the sac (*A*) (fig. 5*a*). The line (*C*) indicates the normal level of the mercury. The reason that the pressure from the sac (*A*) is greater than that in the remainder of the system is because it takes a greater amount of pressure to distend the sac (*A*) than it takes to distend the diaphragm (*B*). With the apparatus as shown in figure 5*a*, if pressure is applied to the diaphragm (*B*), the mercury will rise in both manometers to exactly the same degree (fig. 5*b*, *D*); that is, the increment of rise in each manometer is always the same regardless of the amount of pressure applied to *B*.

This observation can be applied clinically as follows: If a patient is suffering from a gastric ulcer and the stomach is distended forcibly with gas or other fluid, but not forcibly enough to rupture the ulcer, and the patient by some means increases his intra-abdominal pressure, the relative pressure on each side of the ulcer remains the same. In other words, if the distention by gas or other fluids did not cause a rupture, an increase in intra-abdominal pressure would not cause a rupture.

*Observation 12.*—Similar tests were made with the two rubber bags as shown in figure 2*a*, and the same results were obtained.

This principle is not only true for the stomach, but for all of the intra-abdominal hollow viscera.

*Observation 13.*—By continued inflation of the sac (*A*) it can finally be made to rupture, but the pressure required is greater when the sac is in the closed apparatus than when the same type of sac is in the open air.

EXPERIMENT 6.—In this experiment the apparatus used consisted of two transparent balloons of different sizes, one placed inside the other. Each balloon was connected to a manometer. In this experiment the mercury manometers were rather difficult to handle; so the manometers from an apparatus for the determination of blood pressure were used. A T-tube was inserted between each balloon and the manometer to be used for inflation.<sup>2</sup> The assembled apparatus is represented by the solid lines in figure 6*a*.

*Observation 14.*—With the apparatus at rest both balloons assumed the spherical form, and the pressure in the external balloon (*B*) registered 20 while the pressure in the internal balloon (*A*) registered 40.

Pressure on the external balloon made it assume an oval form, and the pressure in each manometer rose to an exactly equal degree. In other words, pressure on the outer balloon caused an equal rise in pressure in the internal balloon, a phe-

2. In testing the degree of pressure required to inflate balloons of various sizes, it was found that the smaller balloons required a greater amount of pressure to inflate them to a moderate size than did the larger balloons. This difference is most probably due to the difference in the tensile strength of the two sizes of balloons. This has no bearing on the present problem, however, as this problem does not concern actual pressures but the relative changes in pressure following the application of external force.

phenomenon exactly similar to that observed in figure 5. The pressure on both sides of the wall of the inner balloon was relatively the same no matter how much pressure was applied to the outer balloon so long as the walls of the outer balloon did not touch the walls of the inner.

*Observation 15.*—No matter how much the outer balloon was compressed or distorted, so long as it did not touch the inner balloon the inner balloon remained a perfect sphere and, as far as the eye could determine, did not change its size.

*Observation 16.*—When the pressure over the outer balloon was continued, the pressure in both balloons rose to the same degree, but as soon as the outer balloon was compressed to the degree that its walls touched the inner balloon and the shape of the inner balloon was in the least distorted or compressed, the pressure in the inner balloon immediately rose at a greater rate than the pressure in the outer. As the pressure continued, distorting both the outer and the inner balloon,

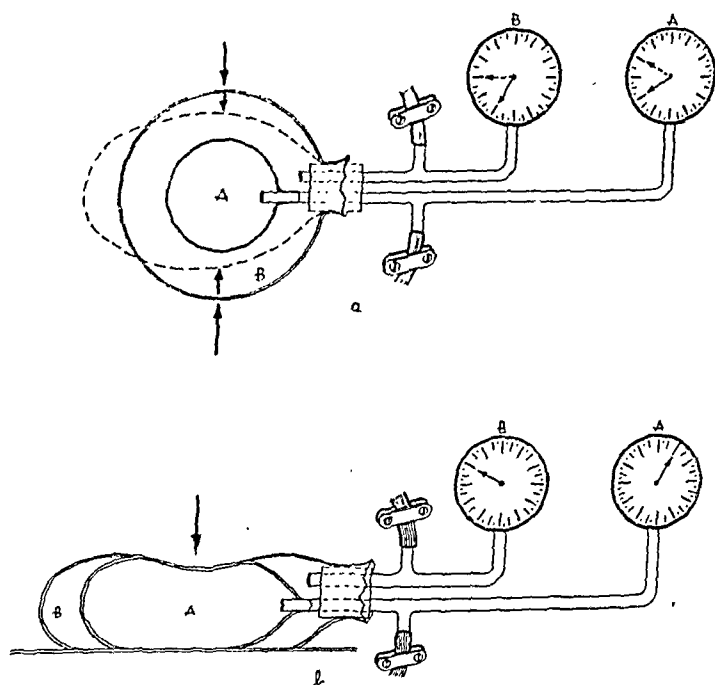


Fig. 6.—Diagrammatic representation of experiment 6.

the pressure in both manometers increased, but this increase in pressure was much more rapid in the inner than in the outer one. In fact, with this increasing pressure with distortion of both balloons, the increase in pressure of the inner compared to the increase in pressure of the outer balloon is approximately in the ratio of an arithmetical progression (fig. 6 b).

When the pressure is continued over the inner balloon through the walls of the outer balloon, the inner balloon finally ruptures.

The experiments shown in figure 6 demonstrate that when one flexible elastic compartment is contained in another larger flexible elastic compartment, it is impossible to rupture the inner compartment by pressure on the outer until the pressure on the outer compartment is sufficient to compress or distort the outer compartment sufficiently to distort or compress directly the inner compartment. In other words, in order to rupture the inner compartment, the pressure must be applied directly to its walls with no interposing fluid. Again, for the inner com-

partment to be ruptured, it must be compressed sufficiently to produce internal pressure beyond its limits of elasticity in the same manner as if it were not surrounded with an outer compartment. The only difference in the rupture of the inner balloon as shown in figure 6*b* and a similar balloon not inside a second balloon is that it takes a greater amount of pressure to rupture the inner balloon than a similar balloon in the open air.

### CONCLUSIONS

From the foregoing observations I believe that the following clinical conclusions can be deduced :

1. Anything that increases intra-abdominal pressure, such as muscular strains requiring the contraction of the abdominal muscles, coughing, sneezing, vomiting, blows or pressure exerted from the outside on the abdominal wall and distention of the abdominal viscera by either fluid or solid matter, tends to exert pressure equally over the entire abdominal wall, and if there are one or more points weaker than the rest of the abdominal wall, there will be a tendency toward the occurrence of hernia at these weakened areas.

2. The inflation or overdistention of a hollow viscus may lead to the rupture of that viscus if the internal pressure is sufficient to overcome the limit of elasticity of the viscus.

3. An increase in intra-abdominal pressure, such as is caused by muscle strains, pressure or blows over the abdomen, causes an instantaneous and equal increase in the pressure in the intra-abdominal hollow viscera, unless a viscus is distended to the point that its walls reach from the abdominal wall in front to the solid tissues on the posterior abdominal wall.

4. If an intra-abdominal hollow viscus is overdistended from within and there follows an increase in the intra-abdominal pressure, the relative pressure on both sides of the wall remains the same.

5. To cause rupture of any intra-abdominal hollow viscus by external force or pressure, this viscus must be distended so that its walls reach the opposite sides of the abdominal cavity, and the blow, force or compression must be directed over the distended viscus.

In other words, for rupture of a normal or a diseased stomach to be produced by violence, the stomach must be distended so that it can be compressed between the anterior abdominal wall and the vertebral column or between the lateral surfaces of the abdomen, and the direction of the violence must be directly over the stomach.

In order to produce rupture of the urinary bladder, it must be distended so that it can be compressed between the abdominal and pelvic walls, and the line of force must be directly over the bladder.

The same holds true for the small intestines, except that these tubes are often empty or are emptied by the abdominal force, in which case



the intestines may be crushed between the anterior abdominal wall and the bodies of the vertebrae in the same manner that a solid organ may be crushed.

The appendix, either normal or diseased, acts similarly to other intra-abdominal hollow organs. It is inconceivable that an appendix could in any way be affected by any increase in intra-abdominal pressure, such as strains, blows or compressions, unless there were a distended appendix superimposed by a mass of solid adhesions that extended to the anterior abdominal wall.

In order, therefore, for an intra-abdominal hollow viscus to be injured or ruptured it must be subjected to the same force that would be required to rupture it if the entire anterior abdominal wall were removed.

In the case of external hernial sacs in the abdominal wall, an increase in the intra-abdominal pressure will tend to force abdominal contents into these empty sacs, owing to the fact that the pressure on the outside of the sac is less than the intra-abdominal pressure on the inside. But internal hernias cannot result from increased intra-abdominal pressure, and loops of intestines, the appendix and other structures cannot be forced under bands or through apertures, because according to Pascal's law the pressure is equal in all directions, and any pressure, no matter how applied, would have the same tendency to push the structure or organ away from the aperture as to force the organ toward the aperture.

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## ELECTRIC SHOCK

PRESENTATION OF CASES AND REVIEW OF THE LITERATURE

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The electric current has always been a source of danger to man. Lightning alone constituted the electric danger of antiquity, responsible for many deaths by a current estimated at millions of volts and about 20,000 amperes. Apparently there were no serious effects from synthetic electricity until 1879, when a stage carpenter was electrocuted at Lyons by an alternating current of 250 volts from a Siemens dynamo and died in twenty minutes. Currents dangerous enough to kill, however, were used as far back as 1849 to light a stage in Paris. The use of electricity in the home, office and factory has increased to such a tremendous extent that energized wires now form a dangerous and intricate network, surrounding one at every turn.

### FACTORS INFLUENCING THE BIOLOGIC EFFECTS OF THE ELECTRIC CURRENT

In discussing the biologic effects of the electric current, I am primarily interested in unconsciousness and burns. Shocks too small to produce unconsciousness, if not often repeated<sup>1</sup> are usually not important from a clinical standpoint unless accompanied by burns. The prime issue in electric shock is the unconscious victim, for here, at a moment, a life is seriously threatened or already spent. The effect which a certain current will have on an organism will depend on the following factors: (1) tension or voltage, (2) intensity or amperage, (3) type of current, (4) resistance at the points of contact, (5) path of the current and (6) individual susceptibility of the organism.

1. *Voltage*.—Death may be produced by currents of very low voltage. There are instances of death from alternating currents of 46 and 60 volts, and it is claimed that any current over 25 volts should be considered dangerous to life. On the basis of the experimental work of Prevost and Battelli and Cunningham, it is now generally conceded that, with currents alternating at ordinary rates (from 25 to 300 per minute), voltages under 220 tend to produce ventricular fibrillation

1. MacMahon, H. E.: Electrical Shock, *Am. J. Path.* 5:333, 1929.

without affecting the respiratory center, those over 1,000 tend to produce paralysis of the respiratory center without affecting the heart and those between 220 and 1,000 tend to involve both the ventricles and the respiratory center. Other things being equal, high tension currents are less dangerous than low tension ones. In one series of electric accidents<sup>2</sup> 62.5 per cent of those who received high tension shocks recovered, whereas only 39 per cent of those who received low tension shocks recovered. It is thus apparent that the voltages in most common use are most dangerous.

2. *Amperage*.—The amperage is computed by dividing the voltage by the resistance. On experimental grounds it is held that an alternating current of from 70 to 110 ma., at ordinary frequencies, or a direct current of from 200 to 250 ma. may be fatal if passed through the chest. Currents of much greater amperage are less often fatal. An alternating current of from 5 to 8 amperes may pass through the body for many seconds without causing permanent arrest of the heart, as is shown by the phenomena attending legal electrocution. In electric accidents the amperage is difficult to determine because of the variable resistance of the body. A slowly alternating current of 30 ma. has been passed through the human chest without any effect on the heart.<sup>3</sup>

3. *Type of Current*.—Alternating currents are said to be from three to four times more dangerous than direct currents. Recent experiments on rats<sup>4</sup> do not confirm this, but one must consider that the rat recovers spontaneously from ventricular fibrillation and that mortality statistics vary with different experimental animals. However, direct currents induce a much more intense nervous inhibition and produce cardiac fibrillation in a much shorter time. In certain experiments on rats alternating current was more apt to produce hemorrhage than direct current, yet the latter was more destructive to nerve cells. Alternating currents of from 39 to 150 cycles are the most dangerous and, unfortunately, the most frequently used. As the number of cycles increases, the danger diminishes. Experiment has shown that the dog's heart is about twenty times as tolerant to an alternating current of 1,720 cycles as to one of 150 cycles; and currents of from 400,000 to 1,000,000 cycles up to 3 amperes have no bad effects. In diathermy, for example, a current of about 20,000 to 40,000 volts, from 1 to 8 amperes and 1,000,000 cycles is employed.

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2. Legge, T. M.; Ram, S.; Levy, A. G., and MacWilliam, J. H.: *The Pathological Changes Produced in Those Rendered Insensible by Electric Shock and the Treatment in Such Cases*, Arch. Radiol. & Electroth. **27**:1, 1922.

3. Jex-Blake: *Death by Electric Current and by Lightning*, Brit. M. J. **1**:425, 492 and 548, 1913. This article gives an excellent review of the subject to 1913.

4. Langworthy, O., and Kouwenhoven, W. B.: *Experimental Study of Abnormalities Produced in the Organism by Electricity*, J. Indust. Hyg. **12**:31, 1930.

Experiment indicates that currents from induction coils are not especially dangerous to man. Spark discharges from condensers are capable of producing fatal effects by inhibition of the respiratory center without any appreciable effect on the heart. It seems that the heart is not thrown into fibrillation by "single" shocks unless the organ is struck at the exact moment when the refractory period ends, and it may be assumed that a person may withstand a powerful "single" shock, unless the heart is struck at this transient phase of its cycle. Prevost and Battelli conclude from their experiments that with very brief shocks from condensers and induction coils (1/1,000 second) fatal effects are due, not to the pressure or intensity of the current, but to the electric energy as measured in joules.<sup>3</sup> In some of their experimental animals an occasional postmortem finding was loss of elasticity and retractility of the lungs, which made recovery on artificial respiration impossible. In another series, the same authors electrocuted dogs with discharges from induction coils giving sparks from 15 to 45 cm. long, and noted that larger animals were killed only by asphyxia. It was their impression that the largest coil would require a minimum exposure of two minutes to kill an adult human being and that death would occur from arrest of respiration without primary heart failure. Single discharges of appropriate energy have restored normal rhythm to ventricles of animals fibrillating experimentally from alternating or direct currents. The following cases show the ability of man to escape unharmed from contact with single high voltage discharges:

CASE 1.—A laborer working in the neighborhood of a large condenser disregarded the danger signs and was struck by a static discharge of 180,000 volts. He was rendered unconscious. Artificial respiration was given at once and he was revived in nine minutes. There were no sequelae.

CASE 2.—A lineman was working on a set of "dead" lines, consisting of three parallel wires about 1 foot (30 cm.) apart. These wires paralleled another set about 15 feet (457 cm.) away, carrying a tension of 110,000 volts. The workman received a severe shock from the current induced in the "dead" line, but was not rendered unconscious. He sustained severe burns of the chest, hands and legs.

CASE 3.—An operator of a discharge set was struck by a single discharge of 150,000 volts, and was rendered unconscious. After thirteen minutes of artificial respiration he was revived. There were no sequelae.

Whenever the flow of the electric current is broken abruptly there is generated in the circuit an electromotive force of the same direction as the original current flow. While the original current diminishes, the development of this "extra current" and its addition to the original current then present increases the total electromotive force. If, in the closed circuit, the voltage is too low or the body resistance too high to produce fibrillation, such a result may follow the action of the extra current when the circuit is broken. On the other hand, the extra

current may be life-saving. Thus, in guinea-pigs, fibrillation induced by a direct current of 550 volts can be relieved by the extra current when the circuit is abruptly broken.

4. *Resistance at the Points of Contact.*—The effect of the current on the body depends to a great extent on the resistance of the skin, since the resistance of the other tissues, with the exception of bone, is small in comparison. The resistance of the skin depends on its condition of dryness, cleanliness and thickness. In a calloused palm, for example, it may reach 1,000,000 ohms and more, but in general, the average resistance of the dry skin is about 5,000 ohms, and that of the moist skin about 1,000 ohms.<sup>5</sup> Thus a current of 100 volts passed through the chest through moist contacts is sufficient to reach the dangerous 100 ma. range inside the body. Perspiration reduces the resistance of the skin considerably. With saline electrodes the resistance of the skin may fall to 300 ohms, and a current of only 30 volts passed through the chest may kill by reaching the fatal amperage. Deaths have been reported from sinusoidal currents, which are slowly alternating currents of from 30 to 50 volts. A high tension current that ordinarily would fail to produce fibrillation may be reduced by a high resistance to such a level as to bring this about.

In considering the resistance of the body, the point of exit as well as the point of entrance is significant. Many accidents occur as the result of good contact with the ground. Shoes have a high resistance when dry, but when wet their resistance is so diminished that a current may traverse the body and cause death. Shoes shod with iron nails are particularly dangerous, especially when the ends of the nails have worn through the inner sole. One should remember that concrete, especially if reenforced, is a good conductor.

The area and firmness of contact are other important factors. A broad surface and firm contact permit the flow of more current at given values than smaller and lighter contacts. As a current passes through the tissues their resistance diminishes rapidly.

Whenever a current flows through a conductor, heat is generated. This varies directly with the resistance and with the square of the current. The skin is the most resistant tissue of the body and is therefore subject to a variable degree of heat at both the points of entrance and exit of the current, thus producing local burns and marks. These will be considered later.

5. *Path of the Current.*—The heart is the danger area in electric shock. The central nervous system is a secondary danger zone, but in accidental electrocutions nearly all currents which traverse the head

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5. Gaby, R. E.: *Electrical Burns and Electrical Shock*, Canad. M. A. J. 17: 1343, 1927.

also pass through the chest. Currents from foot to foot are never fatal per se, no matter how great the current; yet even a small current passed through the chest may cause death. Schridde,<sup>6</sup> in thirty-seven postmortem examinations of persons killed by currents not greater than 250 volts, found electric burns on the left hand in 90 per cent. The conductivity of different organs varies according to their chemical and physical constitution. The blood and lymph streams are the best conductors.

*6. Individual Susceptibility of the Organism Under Various Conditions.*—It has been said that an alert person can tolerate a stronger shock than one taken unawares. It has also been claimed that sleep and anesthesia protect against currents, but this has received no experimental confirmation. Recent experiments on rats<sup>4</sup> indicate, in fact, that the mortality is definitely greater under general anesthesia, and that the death rate increases in direct proportion to the depth of the anesthesia, other things being equal. The view that fright increases the susceptibility to the electric current<sup>7</sup> has not been substantiated. Experiment has demonstrated that fatigue increases the susceptibility to electricity,<sup>8</sup> and this was confirmed by statistics, which showed that in man the greater number of electric accidents occurred at the periods of maximum fatigue (chart).

The part played by preexisting disease in the mortality from electric shock is difficult to estimate. It is known that people with disease of the heart can withstand severe electric shocks (Jellinek).

*7. Duration of Contact.*—The more prolonged the contact the more serious the effect. This is true no matter what the type of current, the nature of the contact or the resistance.

#### DEATH DUE TO THE ELECTRIC CURRENT

It has long been felt that the problems of electric shock might be solved by a study of electric death. Experiment has shown that death from the electric current may occur (1) from primary fibrillation of the ventricles, (2) from failure of the respiratory center, (3) from ventricular fibrillation combined with paralysis of the respiratory center, (4) from prolonged tetanus of the respiratory musculature or (5) suddenly some time later—"Delayed Death."

*1. Ventricular Fibrillation.*—Experiment has given some valuable information regarding ventricular fibrillation. The susceptibility of

6. Schridde, H.: Death from Electric Current, J. Indust. Hyg. 8:58, 1926.

7. Jellinek, S.: Rescue Work in Electrical Accidents, J. Indust. Hyg. 9:214, 1927.

8. Aiello, G.: The Influence of the Vegetative Nervous System and of Fatigue on Susceptibility to the Electric Current, J. Indust. Hyg. 7:43, 1925.

various species to the electric current is quite variable. The frog cannot be killed by any current, no matter how great, unless as the result of burns. Spontaneous recovery from electrically induced fibrillation is the rule in the rat and the rabbit, and occurs occasionally in the guinea-pig. There are, however, no cases of spontaneous recovery in the adult horse, dog or ape. Young animals recover more readily than adult ones. In the cat, direct cardiac massage will almost always restore a fibrillating ventricle to normal rhythm. In the fowl, ventricular fibrillation, once established, can be restored only by passing a current through the chest from back to breast.

By direct cardiac massage combined with artificial respiration, d'Halluin<sup>9</sup> restored normal rhythm to 37 per cent of dogs' hearts in

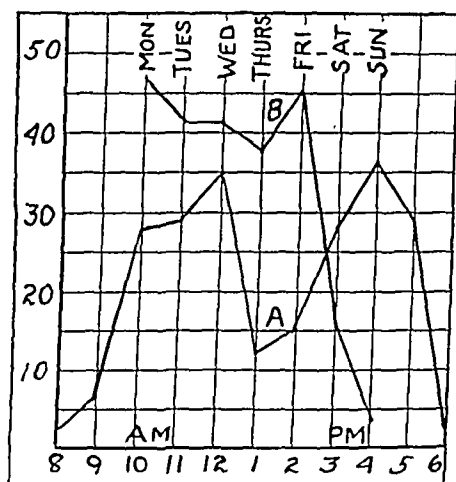


Chart showing the number of electric accidents to be greatest at the periods of maximum fatigue. (From the serial report of the Accident Prevention Committee 1927-1928. Reproduced by permission of the National Electric Light Association.) The accidents, numbering two hundred and thirty-two, occurred in inside electrical construction. A indicates occurrence by hours; B, occurrence by days.

which ventricular fibrillation had been electrically induced. Sixty-five per cent were revived by injecting into the jugular vein 4 cc. of 5 per cent potassium chloride per kilogram of body weight. The toxicity of this drug depends more on the rate of injection than on the dose. According to d'Halluin the lethal dose in dogs is 140 mg. per kilogram at 20 mg. per minute, but is 420 mg. at 4 mg. per minute. Some of the hearts in this series had been quiescent for from ten to fifteen minutes before attempts at restoration were instituted.

9. d'Halluin, M.: Lethal Power of Electricity, *J. de radiol. et d'électrol.* 4:254, 1920.

Hooker, however, was able to revive dogs' hearts without the use of cardiac massage by administering potassium and calcium solutions by the arterial route. One solution consisted of 0.5 per cent potassium chloride in physiologic solution of sodium chloride to which was added 0.025 Gm. of heparin per cubic centimeter to prevent coagulation of the blood. The dose was 13 cm. per kilogram. The other solution was 0.023 Gm. of calcium chloride in physiologic solution of sodium chloride. Its dose was 15 cc. per kilogram. Fibrillation was induced and the potassium solution administered through a cannula. Needles were found to be unsatisfactory because they were too small. The heart came to rest. The calcium solution was then injected through the cannula. Normal rhythm resulted in many cases. Sometimes 1 cc. of 1:1,000 epinephrine was injected into the cannula before the calcium was administered. The femoral artery was successfully used on two occasions. Both solutions were saturated with oxygen, warmed to 37 C. and injected at a pressure of 150 mm. of mercury. Complete recovery ensued ten and one-half and twelve and one-quarter minutes respectively following the onset of fibrillation.

Wiggers<sup>10</sup> studied the effect of potassium chloride in relieving experimental fibrillation induced in dogs by the faradic current. The duration of untreated fibrillation was from fifteen to thirty minutes, a period much in excess of the viability of nerve centers deprived of oxygenated blood. No animals recovered spontaneously. He confirmed the effect of 5 per cent potassium chloride (in salt solution) in abolishing fibrillation in dogs, noting that the drug was most effective if injected, in equal amounts, directly into both ventricles. By electrocardiography Wiggers showed that the drug shortened the duration of fibrillation to three minutes without in any other way changing its character. If into the resting ventricles was injected a similar dose of 5 per cent calcium chloride and the heart massaged at once, coordinated rhythm could be reestablished, the heart first passing through a few minutes of idioventricular rhythm. No drug was effective without cardiac massage.

Prevost and Battelli, using dogs, succeeded in restoring fibrillating hearts to normal rhythm by passing through the organ within from fifteen to thirty seconds an alternating current of greater voltage than that used to produce the fibrillation. In quiescent hearts they were often able to produce ventricular fibrillation by direct cardiac massage

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10. Wiggers, C. J.: Ventricular Fibrillation Caused by Electrical Shock: Revival by Successive Use of Potassium and Calcium Salts, *Am. J. Physiol.* **92**: 223, 1930; Ventricular Fibrillation Caused by Electric Shock: Revival by Successive Use of Potassium and Calcium Salts, *ibid.* **93**:197, 1930. Wiggers, C. J.; Bell, J. R., and Paine, M.: Ventricular Fibrillation Caused by Electric Shock, *Am. Heart J.* **5**:351 (Feb.) 1930.



combined with artificial respiration; then the fibrillation was changed to normal rhythm by passing a current at higher voltage through the heart.

There is a well grounded view that in man, in the majority of cases, death from electric shock occurs as the result of uncomplicated ventricular fibrillation,<sup>11</sup> and that fibrillation once established is usually permanent. Kerr and Bender<sup>12</sup> have reported a single case in which they demonstrated that recovery from ventricular fibrillation may occur spontaneously in man. Others have suggested that spontaneous recovery from fibrillation induced by electricity probably occurs frequently in man, as in some experimental animals. This, however, must be extremely rare, considering the small number of reported cases of recovery from ventricular fibrillation from other causes. In order that the patient survive, a return to normal rhythm must occur within the period that nerve centers can withstand the lack of oxygenated blood, variously estimated at from two to ten minutes. When fibrillation occurs, respirations continue, become exaggerated from asphyxia and then fail after about two minutes, death ensuing. There is no evidence of cardiac function and the patient is pale, not cyanotic.

2. *Failure of the Respiratory Center.*—When the respiratory center alone is affected the victim is unconscious, with respirations absent, but the heart continues to beat. There is a great fall in blood pressure, and the skin is cold and cyanotic. In animals, when no treatment is instituted, the heart will continue to beat for from five to eight minutes after respirations have ceased. It is probable that nervous degenerations of an irrevocable nature may not occur for an equal period following cessation of the heart beat. A similar condition may be expected in man.

In 1912 Jellinek, who had had a vast experience in electric accidents, claimed that in most cases death from electric shock was only apparent. He claimed that these victims suffered from temporary paralysis of the respiratory center and that if the blood were kept properly oxygenated by the use of artificial respiration until the normal irritability of the respiratory center returned, most of the victims would recover. Many others<sup>13</sup> have adopted this view. It was

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11. Aiello, G.: *Electricity and Man*, J. Indust. Hyg. **11**:100, 1929. Legge, T. M., et al.: *Pathological Changes Produced in Subjects Rendered Unconscious by Electrical Shock*, Proc. Roy. Soc. Med. (Sect. Electroth.) **15**:43, 1921; Jex-Blake.<sup>3</sup> Legge, Ram, Levy and MacWilliam.<sup>2</sup>

12. Kerr, W. J., and Bender, W.: *Paroxysmal Ventricular Fibrillation with Cardiac Recovery*, Heart **9**:269, 1922.

13. (a) Report by Engineering Committee of Conference on Electric Shock; *Fatal Accidents from Electric Shock in Recent Years in the United States and Canada, in England and Wales and in Switzerland*, J. Indust. Hyg. **10**:111 and 117, 1928. (b) Harrison, B. J.: *Some Considerations in Death from Electrical Shock*, M. J. Australia **2**:106, 1925; (c) *Electrical Accidents*, *ibid.* **2**:439, 1927.

probably in cases of pure respiratory paralysis that artificial respiration accomplished its spectacular results, one patient having been revived after eight hours, and several after four hours, of so-called "suspended animation."

3. *Failure of the Heart Plus Failure of Respiration.*—When this condition occurs, the picture presented is a combination of those due to respiratory and cardiac paralysis. There is no evidence of breathing or of heart action, and the patient dies within a few minutes.

4. *Prolonged Tetanus of the Respiratory Muscles.*—During the passage of a current through the body, there is a violent contraction of all the muscles until the circuit is broken. If the current continues for many minutes, the patient will die of asphyxia, owing to his inability to use the respiratory muscles, even though the respiratory center and heart might have been capable of functioning properly had the duration of the contact been less prolonged.

5. *Delayed Death.*—Patients who have been revived sometimes die suddenly without apparent cause. This may occur minutes, hours or even days after the accident. It is thought by some to be due to sudden dilatation of the cardiac musculature and by others to be the result of hemorrhage affecting the vital centers. The following is an authentic case of delayed death:

CASE 4.—Two men were working on a "dead" line. Both were standing on the ground. A was steadying the wire with both hands, while B held the wire in his left hand and with his right was tapping a wire clamp to tighten it. Suddenly the wire became energized. Both men were thrown 15 feet, landing in the prone position. There were no injuries to the head or other parts of the body, and both men retained consciousness. A rose, walked 200 feet (61 meters) to his automobile, rode for half a mile to turn off the circuit and immediately returned. B is said to have sat still for six or seven minutes; he then rose, dusted his clothes, drew up his trousers, walked nine steps and fell dead. When A returned, his partner was dead.

#### LOCAL EFFECTS OF THE CURRENT

1. *Electric "Marks."*—Local changes occur at the points of entrance and exit of the current. The most interesting of these are the so-called "current marks." These are produced at the moment the body becomes energized, whether the victim survives or not, and are the same whether produced by direct or alternating current.<sup>14</sup> The marks are usually round or oval, varying in size from a few millimeters to several centimeters in diameter, gray to grayish yellow and slightly elevated at the edges, with a crater in the center. At the point of exit the depression

14. Jaffe, R. H.: Electropathology, Arch. Path. 5:837 (May) 1928. A generous bibliography to 1928 is appended.

is often charred and tends to bleed. The hairs in the vicinity are not affected. The lesions are odorless, painless, free from inflammatory reaction or blisters and remain unchanged for several weeks. After a slow process of aseptic necrosis, sloughing occurs, leaving a luxurious granulation tissue, which finally forms a smooth, pink scar. The resultant slough is from two to three times the extent of the original injury. These marks are considered by some to be the most characteristic manifestations of electric shock and are especially significant when they appear in an area covered by unaffected clothing. It is probable that heat rather than electrolysis is the cause of these marks.

2. *Arc Burns*.—The flash or arc burn represents the most serious of electric burns, and occurs with light or brushing contacts. The arc has a temperature of from 2,500 to 3,000 C., and is capable of melting and volatilizing bone,<sup>14a</sup> producing extensive lesions which may involve entire extremities. When such arcing has occurred, metallic deposits are found around and embedded in the burned area. Charring tends to minimize the general effect by reducing the flow of current through the body. In general, if the resistance at the points of contact is low, general effects are severe and burns slight; if the resistance is high, burns are severe and general effects slight. The final slough is usually more extensive than the original burn, and it is difficult to estimate the extent of the destructive process. Disintegration of the media of the arteries, without involvement of the intima, is probably responsible in part for this destruction, as well as for the occasional occurrence of hemorrhage and necrosis, even some distance from the original site of the injury.<sup>15</sup>

3. *Localized Edema*.—In rare instances the current produces a localized edema, which readily subsides. This may occur without the association of burns.

#### PATHOLOGY

In comparison with the profound clinical disturbances occurring in electric shock, postmortem evidence as to the exact mechanism involved has been disappointing. Certain changes occur, however, with unusual frequency. The vascular changes have already been noted. The arteries are sometimes so friable that ligation is impossible. Experiment indicates<sup>16</sup> that these effects are due to heat and not to some specific action of the current. The muscle fibers of the

14a. Lewis, Dean: Electric Burn Causing Necrosis of the Skull, *Ann. Surg.* 58:149, 1918.

15. Martin: Vascular Lesions from Live Wire, *J. Indust. Hyg.* 6:96, 1924.

16. Jaffe, R. H.; Willis, D., and Bachem, A.: The Effect of Electric Currents on the Arteries: Histologic Study, *Arch. Path.* 7:244 (Feb.) 1929.

media, being the most sensitive part of the vessel wall, are most profoundly affected, and the cooling effect of the circulating blood protects the intima, and to a lesser degree the remainder of the wall. There is no thrombosis and no defense reaction. The blood is of a low viscosity in electric shock.

When very large currents are passed through the body, as in legal electrocutions, capillary hemorrhages are found in the brain and in the floor of the fourth ventricle. These currents, however, are far greater than those necessary to produce death. The hemorrhages in the central nervous system are not found when death is produced by smaller currents. MacMahon<sup>1</sup> demonstrated that destructive lesions were regularly produced in the nervous system and skeletal muscle of animals by repeated sublethal shocks. The question arises as to the possibility of permanent damage to the nervous system in those who, in their work, habitually allow electric current to pass through them. Pathologists are not in agreement as to the significance of certain other microscopic changes sometimes noted in the central nervous system. It is difficult to determine whether these minute alterations are due to artefact, postmortem changes or the effect of the current.

Albuminuria is frequent after electric shock, and usually disappears after the third day.<sup>14</sup> Casts may also be present. Hemoglobinuria is rather common. Jaffe thinks that the albumin and casts are due to toxic products of abnormal protein cleavage.

Few data are available regarding the effect of the current on the pulmonary system. In fatal cases hyperemia and edema of the lungs are at times present (Balthazard, Jellinek, Verse). Schridde<sup>6</sup> noted moderate edema of the lungs in 56 per cent of thirty-seven fatal accidents from low voltage currents. These findings have been supposed by Naville and deMoisier to be due to the original arterial hypertension, causing fluid to accumulate in the alveoli. Primary heart failure may also be a factor. The effect of the current on the lungs of those who survive the shock does not seem to be great. I know of no cases of pulmonary disease in revived persons that could be ascribed to the shock, unless as a result of artificial respiration given by mechanical respirators. It is safe to say that at the present time there are no gross or microscopic visceral lesions absolutely indicative of the passage of electricity through the organism or of death from this agent.

#### TREATMENT

The immediate treatment of the unconscious victim is rarely administered by a physician but usually by friends or co-workers. Linemen usually work in pairs, so that a companion, previously trained in

resuscitation, is at hand to give prompt aid in case of accident. The victim should be freed from the current at once. This may have happened spontaneously, owing to the action of certain muscles in throwing him some distance from the conductor as in case 4. Should the victim be at a considerable height from the ground, as is frequently the case with linemen, the fall alone may be the cause of severe injury or death. Again, because of unconsciousness produced by the shock, the victim may spontaneously break the circuit by falling away from the conductor. On the other hand, the action of other muscles may hold him fast to the conductor. This is especially true when the hands act as areas of contact.

The circuit may be broken by throwing the proper switch, if near at hand, or the conductor may be severed by using properly insulated instruments, such as are usually carried by electrical workers, or by using an axe with a dry, wooden handle. The current may be diverted by allowing a metal chain to make simultaneous contact with the conductor and the ground. The charged person may be dragged away from the live line by dry loose clothing or a leather belt, or pushed away by a stick of dry wood or other nonconductor. In touching the charged victim, the rescuer should use the foot, remembering that currents from foot to foot are never fatal per se, whereas those from hand to hand, or hand to foot frequently are. When the circuit is broken with an axe or other cutting instrument, the head should be turned away from the site of contact in order to protect the eyes from the flash which is frequently produced and which may be a source of danger from flash cataract for many months.<sup>17</sup>

CASE 5.—A lineman on a pole, whose leg was grounded through a telephone wire, contacted 4,000 volts with his ear. He fell 20 feet (609 cm.), striking his head on a heavy board. He was unconscious, not breathing, and his pulse was imperceptible. He was immediately given artificial respiration by the prone pressure method, and was revived in forty-two minutes. On the fourth day an exploratory laparotomy was performed for shock and abdominal pain. The intra-abdominal findings were normal. On the fifth day he died. Autopsy disclosed a rupture of the kidney, which was evidently the cause of death.

CASE 6.—A lineman on a pole contacted 4,000 volts with his hands. His fellow workman saw the accident and noted that the victim was unconscious and not breathing. He immediately cut the conductor, catching the victim as he was about to fall. Without attempting to lower him he began to give artificial respiration in an unusual manner. He placed the victim so that the abdomen and chest lay against the pole, and then encircled the pole and the unconscious body with his arms. By pressing and relaxing at regular intervals he induced artificial respiration. The patient was resuscitated in five minutes. Severe burns were present on

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17. Franklin, W. S., and Cordes, F. C.: Electric Cataract, *J. A. M. A.* 85:245 (July 25) 1925. Lewis.<sup>14a</sup>

the right hand and the entire left upper extremity, which later necessitated amputation of the arm. The victim recovered and the rescuer was awarded a gold medal. Had the patient fallen, he might have sustained fatal injuries.

The patient, freed from the contact, may be dazed or he may be unconscious with a normal heart action and respiration. In such cases fresh air and quiet are the only necessary therapeutic measures, with care that no mechanical obstruction to respiration is permitted the unconscious patient. The victim, however, may be unconscious and not breathing, but with the pulse still present; there may be no evidence of respiration or heart beat, or the victim may give a few gasps and then show no signs of respiration or pulse. Any unconscious victim who is not breathing should immediately be given artificial respiration, to be continued without interruption until spontaneous respirations are resumed or death is certain. Jex-Blake,<sup>3</sup> despite his opinion that the majority of cases are due to ventricular fibrillation, warns that "only the cooling of the body or the onset of rigor mortis should be considered as evidence of death."

The prone pressure method of Schaefer<sup>15</sup> is without doubt the best method of artificial respiration and superior to the mechanical devices such as the pulmotor and lung motor. It has the following advantages: It is simple, is immediately available, needs only one operator at a time, most closely simulates normal respiration and offers less danger of rupturing the lungs and blood vessels. Finton<sup>19</sup> has shown that the Schaefer method induces 105 per cent of the normal air exchange in deep breathing, whereas the Sylvester method induces only 35 per cent. All pressure and suction types of apparatus, in which the regulation of intrapulmonary pressure depends on the operator, no matter what his qualifications are, are dangerous and have long ago been discarded by progressive organizations. I do not doubt that many victims have actually been killed by the very apparatus applied to revive them, since there is no scientific basis of regulating the amount of force to the tolerance of the patient's delicate respiratory system.

The spectacular results of artificial respiration have been a great stimulus to the immediate use of this measure and its faithful application over a period of many hours. It is interesting that persons have been revived hours after an attending physician has pronounced them dead from electric shock, and it has even been claimed that autopsies have been performed on victims in states of "suspended animation."

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18. (a) Drinker, C. K.: Artificial Respiration in Electric Shock and Gas Poisoning, *J. A. M. A.* **83**:764 (Sept. 6) 1924. (b) Henderson, Yandell: Resuscitation, *ibid.* **83**:758 (Sept. 6) 1924.

19. Finton, W. L.: Resuscitation after Electrical Shock, *J. Michigan M. Soc.* **23**:544, 1924.

There is some indication, however, that the value of artificial respiration in electrical unconsciousness may have been considerably overestimated. In my experience, it has been of no avail in the majority of cases, even though given promptly, properly and faithfully by crews specially trained in the Schaefer method.

In the present series of electric accidents, numbering fifty-eight from 1922 to 1930 inclusive, fifty-three of the victims (91 per cent) died. Important additional data were available in only twenty-seven cases. These twenty-seven cases form the basis of the following deductions (table). Twenty-two patients, or 82 per cent, were rendered unconscious by the shock. In one case artificial respiration was not begun for thirty minutes and in another it was begun at once and discontinued after thirty minutes. In all other patients, in whom respirations were absent (74 per cent), artificial respiration by the prone pressure method was begun within a few minutes and continued without interruption until the victim was revived or rigor mortis appeared. In the fatal cases the minimum duration of artificial respiration was four hours and the maximum eleven and a half hours. Twenty-two patients (82 per cent) died. Of these fatalities four (15 per cent) were due to falls and burns. The remainder of the fatalities were due to the current alone (eighteen patients, or 67 per cent). Of these eighteen patients, sixteen probably died of persistent ventricular fibrillation. This represents 89 per cent of deaths due to the current alone and 73 per cent of the total deaths. Uncomplicated paralysis of the respiratory center was probably the cause of death in five patients (18 per cent). These statistics do not agree with those of Drinker and others,<sup>13a</sup> who reported 76 per cent of recoveries in two hundred and sixty-five cases of electric shock.

No amount of artificial respiration will restore to normal rhythm a fibrillating ventricle. None the less it is wise to give this treatment continuously if operation is inadvisable, with the thought in mind that the diagnosis may be wrong or that spontaneous recovery, should it occur, will find the most favorable conditions. I know of no case of recovery from electrically induced unconsciousness in which fibrillation of the ventricles was known to have been present, and my clinical experience confirms the impression gained by experiment, that in the majority of cases death occurs promptly from persistent ventricular fibrillation. The chief problem, therefore, in the treatment of electric shock, concerns the treatment of ventricular fibrillation.

The persons on whom the task of immediate treatment falls are unable to judge the nature of any particular case of electric unconsciousness, and in consequence each case is treated as one of respiratory paralysis. The physician, however, is better qualified to determine the

nature of the electric accident. So long as there is evidence of normal cardiac rhythm, the prognosis is good and artificial respiration should be continued. Once the diagnosis of ventricular fibrillation is certain and artificial respiration has not revived the patient within fifteen minutes after the accident, unduly prolonged artificial respiration is illogical.

The heart sounds may not be audible and the pulse not palpable, yet the heart may be beating feebly. In such cases, however, it is more likely that ventricular fibrillation has been produced. If regular pulsations are noted in the veins of the neck, and no heart movements are heard or felt, ventricular fibrillation is even more likely, as it indicates that the auricles are still functioning rhythmically. The absence of venous pulsations in the neck is not so important, for auricular fibrillation may accompany ventricular fibrillation. The diagnosis is uncertain in most cases. D'Halluin<sup>9</sup> suggested that a drop of ether instilled into one eye will reveal the presence of even a feeble circulation by the redness produced, the other eye serving as a control. During this test the patient should lie horizontal and all other influences which might have a bearing on the interpretation of the result should be excluded. He also suggested that a blunt probe introduced through the skin to lie directly against the ventricle would show the presence or absence of regular pulsations, or possibly the tremulations of a fibrillating heart.

The presence of ventricular fibrillation having been indicated by a careful test, the surgeon is confronted with a most grave situation. The injection into both ventricles of potassium followed by calcium,<sup>10</sup> and the passage through the heart of a current at higher voltage than that used to produce the fibrillation are likely to stop ventricular fibrillation in man. In order to restore regular rhythm, both of these methods require prompt exposure of the heart for direct massage, a heroic measure indeed, which must be performed before the death of the vital centers (ten minutes). The carotid route for the administration of potassium and calcium<sup>20</sup> has been successful in dogs without cardiac massage, and would be worth attempting in human beings. If these measures were unsuccessful, cardiac massage could be resorted to. It is therefore clear that the chance of recovery from ventricular fibrillation occurring under the conditions of electric shock is almost hopeless, practically speaking, unless the accident occurs in a hospital or operating room. In favorable cases the surgeon should not shrink from making a quick, abdominal incision and massaging the heart. One must realize that grave circumstances call for heroic action, and that, in the

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20. Hooker, D. R.: Chemical Factors in Ventricular Fibrillation, *Am. J. Physiol.* **92**:639, 1929; Recovery of the Heart in Electrical Shock, *ibid.* **91**:305, 1930.



# Electric Shock: Record of Cases (1925-1930)

Case	Voltage	Contact Areas	Unconsciousness	Length of Artificial Respiration	Burns	Pulse	Respiration	Additional Data	Final Result
1	4,000	Left shoulder; both feet	Immediate	5 hrs.	.....	0	0	Victim was standing on crossarm of pole	Death; never regained consciousness
2	11,000	Right hand; both feet	Immediate	4 hrs.	.....	0	0	.....	Death; never regained consciousness
3	4,000	Left arm; right leg	Immediate	1½ hrs.; until rigor mortis	Severe; 3d degree at contact areas	0	0	Rigor mortis in 1½ hours.....	Death; never regained consciousness
4	4,000	Left hand; right hand	Immediate	4 hrs.	.....	0	0	Contact made through pliers in right hand to ground wire in left	Death; never regained consciousness
5	?	Hand; both feet	Walked 7 ft., then fell unconscious	7 min.	None	+	0	Very cyanotic; supposedly dead; no sequelae	Recovery
6	4,000	Hand; both feet	Immediate	4¾ hrs.; until rigor mortis	.....	+	0	Beneficial results from use of carbonogen combined with artificial respiration	Death
7	Low voltage; secondary wire from primary of 6,000	Both hands; both feet	Immediate	4 hrs.	3 pinhole-sized "marks" on hands	0	0	.....	Death; never regained consciousness
8	11,000	Both hands; left foot	Immediate	4 hrs.	.....	0	0	.....	Death; never regained consciousness
9	11,000	Right arm; both legs	Immediate	0; respirations present	At contact areas	+	+	Fractures of skull and pelvis from fall	Death 10 hours later, probably from fall
10	?	Face; both feet	Immediate	4 hrs.	.....	0	0	Current traveled 20 feet, through ground to wire fence; victim contacted fence	Death; never regained consciousness
11	11,000	Both hands; knee	Immediate	4 hrs.	.....	0	0	Contact established while splicing wire; wire became energized	Death; never regained consciousness
12	410	Both hands	Not unconscious	0; respirations present	Severe; covered almost entire body	+	+	Contact established while testing 440 volt fuse with lamp; clothes ignited	Death after 16 hours, probably from burns
13	4,000	Right hand; both feet	Immediate	30 min.	.....	..	0	Duration of artificial respiration not sufficient	Death

14	11,000	Right hand; left hand	Unconscious after 30 sec.	2½ hrs., not begun for 30 min.	.....	+	+	Contact established through lead pencil and an electric device	Death
15	11,000	Both legs; back	Not after 1st shock Immediate after 2d shock	4 hrs.	Severe at contact areas	..	..	Two successive shocks; fuse blew out at substation and substation operator reestablished current flow; victim was killed immediately	Death
16	4,000	.....	Not uncon- scious	0; respi- rations present	Severe 3d degree on upper half of body	+	+	Clothes ignited .....	Death 16 hours later, probably from burns
17	4,000	Right arm; right leg	Immediate	4 hrs.	None	0	0	Grounded leg through "green" (wet) pole	Death
18	11,000	.....	Immediate	2½ hrs.	.....	..	..	.....	Death
19	4,000	Ear; leg	Immediate	42 min.	.....	+	0	Laparotomy on fourth day for shock and abdominal pain; autopsy showed rupture of kidney, probably from fall	Recovery after 12 minutes; death after 3 days from rupture of kidney
20	11,000 (?)	Both legs; precordium	Immediate	4 hrs.	Severe at contact areas	0	0	Contact with current induced in "lead" wire paralleling a similar wire carrying 11,000 volts 4 feet away	Death
21	11,000	Right heel; right arm	Immediate	11½ hrs.; until rigor mortis	.....	Slow and weak	0	Apparent death in 10 hours, when pulse became imperceptible	Death
22	4,000	Left arm; both feet	Immediate	4 hrs.	.....	0	0	"Green" pole .....	Death
23	? Induced from 110,000	Chest; hands; legs	Not uncon- scious	Respira- tions present	Severe at contact areas	+	+	.....	Recovery
24	?	.....	Not uncon- scious	Respira- tions present	.....	+	+	Victim thrown 15 feet; stood up, walked ten steps and fell dead	Death delayed for 10 minutes
25	?	.....	Not uncon- scious	Respira- tions present	.....	+	+	Same accident as in case 21; vic- tim thrown 15 feet	Recovery; no sequelae
26	4,000	Both hands; left arm	Immediate	5 min. while on pole	Severe at contact areas	..	0	Severe shock for 36 hours.....	Recovery
27	4,000	Right hand; left foot	Immediate; lasted 30 min.	20 min.	Severe 3d degree at contact areas	..	0	Contact established through brace and bit through "green" pole; 8 weeks' hospitalization because of burns	Recovery; neurotic symptoms

words of d'Halluin,<sup>9</sup> "Un coeur qui tremule n'est pas une coeur mort [A quivering heart is not dead]."

Reports are not wanting in which quiescent or fibrillating human ventricles were revived by prompt cardiac massage. I know of no case of massage of the heart in a human subject for the relief of ventricular fibrillation induced by the electric current, yet the applicability of this procedure, combined with the use of potassium and calcium, as a method of treatment appears to be logical. The heart is best approached through an abdominal incision. The thoracic approach is more dangerous and time-consuming. The organ is grasped through the intact diaphragm. If this is not possible, the diaphragm should be incised near its costal insertion, about 1 inch (2.5 cm.) to the left of the mid-line and the hand introduced through the opening. The heart is grasped between the thumb and the first two fingers and gently but firmly massaged at the rate of about thirty times per minute. If available, calcium chloride may be injected into the ventricles before massage. Even if the heart is at rest, cardiac massage should be instituted, but without the use of potassium chloride. If massage of the quiescent heart produces merely a state of fibrillation, potassium and calcium should be administered as advised, and massage should be continued.

The use of stimulating hypodermics has been discouraged by those most familiar with problems of resuscitation.<sup>21</sup> The intracardiac injection of caffeine, epinephrine or alpha-lobeline has been looked on with favor by some.<sup>22</sup> Lobeline is a dangerous drug,<sup>23</sup> and may even cause the death of a victim who might otherwise have been revived. Caffeine is safer and more efficacious. Inhalation of oxygen alone, or air enriched with oxygen, is not advised because oxygen is not a respiratory stimulant, and may even act as a depressant. The use of carbogen (7 per cent carbon dioxide in oxygen) is of definite value not only in those cases in which respirations have become spontaneous, but also in combination with artificial respiration. Zangger, Israel and others<sup>7</sup> advise faradism of the phrenic nerve as a respiratory stimulant.

CASE 7.—A workman on a pole contacted 4,000 volts. He was immediately rendered unconscious. There was no evidence of pulse or respiration. He was markedly cyanotic. One and a half minutes after the accident artificial respiration was instituted and continued without interruption for about five and one-half hours. For one hour his condition remained unchanged. An inhalator arrived at about

21. McLachlan, W.: Resuscitation After Electrical Shock, *Canad. M. A. J.* **17**:1346, 1927. Drinker,<sup>18a</sup> Henderson,<sup>18b</sup> Finton.<sup>19</sup>

22. Morgan, J. G., and Amor, A. J.: Case of Electrocution With Notes on the Clinical Value of Lobeline, *Lancet* **1**:756, 1928. Jellinek.<sup>7</sup>

23. Drinker, C. K.: Acute Asphyxia as a Medical Problem, *J. A. M. A.* **90**: 1263 (April 21) 1928. Norris, V. H., and Weiss, S.: The Properties of Alpha-Lobeline, *J. Pharmacol. & Exper. Therap.* **31**:43, 1927.

this time. Artificial respiration was then combined with inhalation of carbogen. A few minutes after the use of the gas the color of the patient became quite normal and remained so for forty-five minutes. At this time the supply of carbogen became exhausted. Then the deep cyanosis returned. Fifteen minutes later a second supply of gas arrived, and immediately on using the inhalator the normal color reappeared and remained normal for another forty-five minutes, when this supply became exhausted. Then the cyanosis again returned. Unfortunately no more carbogen was available. The cyanosis continued, despite the use of artificial respiration, until rigor mortis set in about two hours later. One can only conjecture whether or not the victim would have been saved, had sufficient carbogen been available.

It has been believed that if the unconscious victim were subjected to some physical shock he would quickly recover, but experiment has not confirmed this, and "counter-shock" is now considered unjustifiable.<sup>24</sup> Jellinek<sup>25</sup> and others<sup>26</sup> advise lumbar puncture and drainage as a prompt therapeutic measure in cases showing signs of increased intracranial pressure. Such signs may appear at once or hours after the accident. The revived patient should immediately be hospitalized, and kept at rest for at least three weeks to guard against sudden cardiac dilatation or secondary hemorrhage and to give rest to a possibly damaged central nervous system.

Electric burns which during the first twenty-four hours appear trivial may later become serious, even fatal, from toxic absorption, secondary hemorrhage or infection. All electric burns should be treated with care. Those of the first degree may be treated with soothing ointments; in the second and third degree burns greasy ointments are not advised. The less serious second and third degree burns may be treated with radiant light and ultraviolet rays.<sup>27c</sup> In severe second and third degree burns treatment with tannic acid is recommended. In clean cases the coagulum usually separates at about the tenth day. If infection supervenes, an anesthetic should be given and the membrane should be removed under rigid asepsis, the wound thoroughly cleaned, all grease, scabs and debris removed and the wound treated by antiseptics or by radiant light and ultraviolet irradiation. Acriflavine base 1:5,000 is recommended by Fisher.<sup>27</sup> Mercurochrome-220 soluble has been discarded. Beneficial effects are said to follow the local application of

24. Campbell, A., and Hill, L.: Countershock as a Method of Resuscitation Following Electrocution, *J. Indust. Hyg.* 6:267, 1924. Drinker.<sup>18a</sup> Finton.<sup>19</sup>

25. Jellinek, S.: Active Treatment of Wounds Produced by Electricity, *Wien. klin. Wchnschr.* 41:766, 1928. Lumbar Puncture in Electrical Injuries, *J. Indust. Hyg.* 11:80, 1929. Value of Lumbar Puncture in Electrical Shock. *Internat. Clin.* 1:123, 1929; footnote 7.

26. Schneider, P.: Mechanism Involved in Death from Electrical Shock, *J. Indust. Hyg.* 11:216, 1929.

27. Fisher, H. E.: Electrical Burns, *Illinois M. J.* 57:201, 1930.

normal horse serum to which 0.35 per cent cresol has been added.<sup>28</sup> Débridement is best performed after separation of sloughs because of the confusion of fascial planes and the danger of alarming hemorrhage. Skin grafting by full thickness or pedicle grafts may be indicated when the wound is clean and healthy granulations are present.

On the whole surgery should be approached with caution, because of the tendency of the lesions to increase in size and because of the vascular injuries which may extend a considerable distance from the apparent site. On the other hand, Wells<sup>29</sup> recently advised prompt débridement of the burn, followed by an immediate skin graft, claiming that the convalescence is thereby considerably shortened. Although his series is a rather small one from which to make deductions, it appears as if there is merit in his method of procedure in selected cases, provided that the débridement is generous enough to remove all affected tissue. I have had no experience with this method. Prompt application of elastic bandages may be necessary to control hemorrhage from arteries too friable to withstand ligature. Emergency amputation of necrotic extremities is rarely necessary, and should be resorted to only if the patient is critically ill from absorption or infection, and only after all other measures have been tried. Indications for amputation may occur within a few hours after the accident, or only after days or weeks. Rarely is primary suture of nerves or tendons necessary.

#### COMPLICATIONS AND SEQUELAE

In the majority of patients revived from electric shock there are no lasting disturbances. Headache is a common early sequel. Some dilatation of the heart may be present in severe cases. The pulse rate is often slow. There may be inhibition of micturition and marked constipation for many days. In severe cases acute cerebral edema with epileptiform convulsions may appear, and acute pulmonary edema is not uncommon. Paralyzes of various types and grades have also been reported.<sup>30</sup> These are often associated with sensory and reflex disturbances, and they may be transient or permanent. Thompson has reported two cases of internal strabismus, one due to contact of the head with 120 volts, and the other to contact of the mouth with 110 volts.

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28. Monteith, S. R., and Clock R. O.: *The Treatment of Burns With Normal Horse Serum*, J. A. M. A. **92**:1173 (April 16) 1929. Fisher.<sup>27</sup>

29. Wells, D. B.: *Treatment of Electrical Burns by Immediate Resection and Skin Graft*, Ann. Surg. **90**:1069, 1929.

30. Jellinek, S.: *Paralysis of the Radial Nerve and Trophic Disturbances Following an Electrical Burn*, J. Indust. Hyg. **3**:112, 1921-1922. Mendel, K.: *Unilateral Spinal Paralysis from Electrical Injury*, *ibid.* **10**:78, 1928.

At various times reports have been made of the association of cutaneous burns with acute gastro-intestinal ulceration in man. In recent experiments on rats<sup>31</sup> high frequency electric burns were associated quite regularly with ulceration of the gastro-intestinal tract. There were no cases of the so-called "Curling" ulcer in my series. Some of the patients showed gastro-intestinal symptoms of a mild type, which cleared up promptly under the administration of sedatives.

Certain sequelae appear quite late, even in cases in which the shock is more or less slight. Of special interest is the effect of the current on the skeletal system.<sup>32</sup> Jellinek has called attention to certain unusually fine and delicate lines in the roentgenogram, some only 1 mm. long, and difficult to distinguish from the normal bone structure. These lines may not appear for two or three weeks, and may arrange themselves in linear, zigzag or stellate patterns. They constitute the mildest manifestation of the effect of the electricity on living bone. Nothing may happen for weeks or months, and finally an osteoporosis may develop to an extent that spontaneous fractures are produced or sequestrums extruded. Areas of rarefaction in the roentgenogram have been traced back to these early manifestations, which occur most commonly at the contact zones.

Other late sequelae may involve the central nervous system. There may be marked disturbances of the psyche, with feelings of inferiority and impending disaster, insomnia, amnesia, defects in concentration, loss of sexual power and psychoneurotic syndromes such as are seen after cerebral concussion. A great variety of sensory and motor disturbances of the nervous system have been reported, e. g., ascending peripheral neuritis, flaccid paralysis of the extremities, peripheral neuritis of the sensory nerves and choreo-athetotic disturbances. The electric flash may be the cause of photophobia, conjunctivitis, retinitis, disturbances in color vision and even atrophy of the optic nerve. Cataract is an occasional sequel to the electric flash, and the possibility of the development of this condition must be considered for a period of two years after the injury.<sup>17</sup> There may be disturbances in blood pressure owing to the effect of the current on the vasomotor center.<sup>33</sup>

When a worker receives a shock from which he recovers within a few minutes, it is the custom of employers to allow him to continue

31. Baldwin, W. M., and Dondate, M.: High Frequency Burns in Rats, *Proc. Soc. Exper. Biol. & Med.* **27**:65, 1929; Baldwin, W. M., and Nelson, W. C.: Histological Effects Produced in Albino Rats by High Frequency Currents, *ibid.* **26**:589, 1929.

32. Jellinek, S.: Röntgenologische Knochenaufnahmen bei Behandlung elektrischer Unfälle, *Wien. med. Wchnschr.* **79**:543, 1929. Pulugay, J.: Bone Changes After Injury by Electric Current, *J. Indust. Hyg.* **7**:180, 1925.

33. Pfalz, W.: Hypertension After Electrical Injury, *J. Indust. Hyg.* **5**:67, 1923.

with his activities. The complications and sequelae noted should be sufficient warning, however, that every case of electric shock, if at all severe, should be considered as a hospital emergency for several days or until all danger is passed. Victims who have been rendered unconscious, or who have displayed even mild signs of damage to the central nervous system, should be kept at rest for three weeks. Roentgenologic studies of areas which have served as contact poles should be made at regular intervals until all danger of osteoporosis is over.

The victim may be incapacitated for long periods of time as the result of his injury. Especially when psychic disturbances are concerned, one is tempted to brand such patients as malingerers or hysteroneurotic persons. It is often difficult to judge just how much is due to the effect of the current on the body and how much to an attempt on the part of the patient to obtain prolonged compensation. The current is an agent which may produce profound functional changes in the central nervous system, and thus offer difficulty in properly evaluating symptoms which might be ascribed to it.

#### SUMMARY AND CONCLUSIONS

1. The factors which influence the effect of the electric current on the living organism have been considered.
2. The mechanism of the production of death from electricity in man and in animals has been considered and cases have been cited.
3. It is probable that death from electricity in higher animals is due, in a majority of cases, to primary fibrillation of the ventricles. In man this condition is hopeless unless prompt and heroic treatment is instituted.
4. Postmortem findings fail to explain the cause of electric death. Changes in the walls of the vessels are noteworthy. Heat rather than electrolysis is probably responsible for most pathologic changes.
5. The treatment of electrically induced failure of the respiratory center is artificial respiration by the prone pressure method until the victim breathes or until death is certain.
6. The treatment of electrically induced ventricular fibrillation is prompt cardiac massage, preceded if possible by the intraventricular injection of potassium salts followed by calcium salts. The carotid route for the administration of these salts may prove sufficient without the use of cardiac massage. If available, an appropriate current may be passed through the heart, followed by cardiac massage.
7. The value of prolonged artificial respiration as a life-saving measure in unconsciousness produced by the electric current seems to have been overestimated. In 82 per cent of twenty-seven collected cases the patients died despite its use under ideal conditions over long periods of time.

8. Stimulating hypodermics, inhalation of pure oxygen and counter-shock are not advised. Inhalation of carbogen is a valuable aid to artificial respiration. Lumbar puncture has a definite place in the treatment of certain patients.

9. Electric burns may be treated by radiant and ultraviolet irradiation. Ointments and dusting powders are not advised in severe burns. Immediate débridement and skin graft have been successful in a small number of cases. On the whole, surgery should be employed with caution.

10. The sequelae of electric shock are many and varied. The most important ones affect the skeletal and nervous systems.



# CARCINOMA OF THE LIP

## CLINICOPATHOLOGIC ANALYSIS OF SEVENTY-SEVEN CASES AND SUGGESTION FOR RATIONAL PLAN OF TREATMENT

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In a recent review of seventy-seven cases of carcinoma of the lip, several interesting facts were revealed and considered worthy of publication.

Epidermoid carcinoma of the lip comprises from 2 to 3 per cent of all cases of cancer and occurs twelve times as frequently on the lower lip as on the upper.<sup>1</sup> The factor of regional metastasis transforms the primary lesion from a relatively innocuous and curable one to an incurable one in at least 50 per cent of the cases. Metastasis to regional nodes (submental and submaxillary) is an embolic phenomenon. As a rule, metastasis from a cancer of the lower lip appears first in the submental glands and then in the ipsilateral submaxillary glands. However, in many instances the first metastases appear in the contralateral submaxillary glands. The regional glands of the neck present an almost impassable barrier to further metastasis. Remote metastases occur in only about 1 per cent of cases. In general, when death results from cancer of the head and neck, it is because of local and regional development of the disease and not because of distant invasion.

The attitude toward treatment of cancer of the lip has been consistently in favor of some form of radical dissection of regional nodes. However, Bloodgood has recently emphasized the fact that early spinal cell cancer of the lip is seldom associated with metastasis, and that if metastasis is present, it is most frequently a late event.<sup>2</sup> He recommends the cell grading of Broders and McCarthy as valuable in determining the treatment of cancer of the lip.

Dr. Edmund Kelly has studied the results in a large series of patients treated at the Kelly Institute in Baltimore, and briefly sums up his impressions as follows<sup>3</sup>: The cases fall roughly into three groups. In the first group, in which the primary lesion does not involve more than one half of the lip and there is no palpable evidence of metastasis

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From the Department of Surgery, College of Medicine, State University of Iowa.

1. Crile, G. W.: Cancer of the Jaws, Tongue, Cheek and Lips, Surg., Gynec. & Obst. **36**:159 (Feb.) 1923.

2. Bloodgood, J. C.: Cancer of the Lip, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 4, chap. 4, p. 74.

3. Personal communication.

to the glands, more than 95 per cent of complete, permanent cures are obtained with a single treatment with radium. In the second group, in which the primary lesion involves not more than one half of the lip and a few small palpable glands are involved, there are occasionally complete cures and frequently good palliation. In the third group, in which the lesion involves more than one half of the lip or is invading the cheek and is associated with large metastatic glands, no cures are obtained, and palliation is hardly worth while. Dr. Kelly expressed the belief that if small glands are palpable, excision may be advisable. If no glands are palpable, the neck should be spared dissection, since, in his experience, metastasis has almost always occurred late and only after the primary lesion is advanced and secondarily infected.

In general, the cases fall into three groups: Group A consists of those cases in which the patients present epidermoid carcinoma of the lip, with no palpable evidence of glandular metastases. The results of surgical intervention or radium therapy in these cases are uniformly excellent. The reason is obvious and twofold—early attack and accessibility. Which manner of treatment one chooses is essentially of minor consequence. Radium is “easier to take.” On the other hand, by surgical excision the lesion is removed at once and the possibility of leaving a few viable cancer cells lurking in the scar is completely obviated. In addition, excision makes it possible to study the primary lesion microscopically, which, as will be referred to later, I believe is of much more than academic importance.

Group B consists of cases in which there are palpable submaxillary or submental glands which have not become so large and tumefied as to be obviously malignant. It is not to be denied that an attempt to differentiate between inflammatory hyperplasia and glands containing tumor cells will be productive of a large percentage of errors.<sup>4</sup> It is for this reason that statistics concerning this group of cases from a radiologic clinic or, in any event, from a place where microscopic sections are not available, are to be strongly questioned. The present study bears this out. That is, a clinical diagnosis of metastasis has proved to be wrong so much more frequently than the reverse error has been made that, in the absence of microscopic proof, results from radium therapy may seem miraculous but are only misleading. It is this group that deserves the most careful attention and discrimination. Our results are in accord with those of Dr. Bloodgood, who stated that much unnecessary surgical intervention is done in these cases.

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4. In order to have a more accurate record of these cases for purposes of subsequent study, a pictorial form has been introduced. See figure 1 in connection with case report of G. O. (case 25). Such a diagram might be of value to the surgeon as a record, and in teaching hospitals should represent the composite opinion of all the members of the staff at the time when general rounds are made.

Our records show that altogether too large a proportion of patients have been subjected unnecessarily to a bilateral block dissection of the submaxillary regions, including the submaxillary salivary glands. It might be argued that chances should not be taken. The operative field is a vascular one; healing is good, and no untoward results seem to occur from the loss of both submaxillary salivary glands. If this were true, it would still not meet the endorsement of good surgical

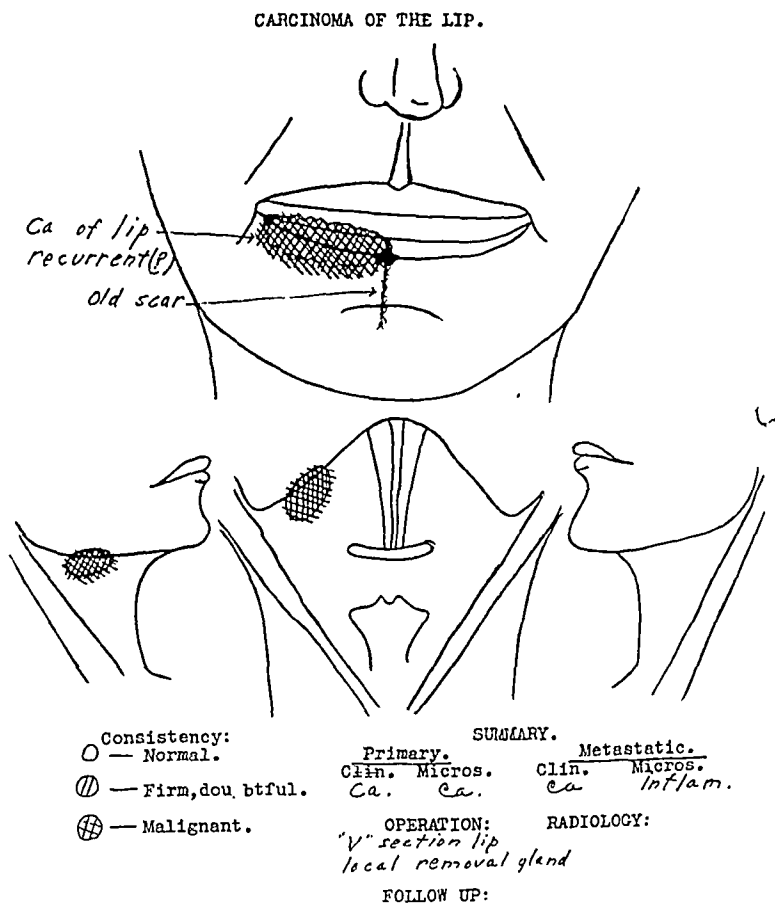


Fig. 1.—Diagram for case 25, illustrating value of pictorial form as a record and its use in teaching.

practice. More careful discrimination leading to the preservation of tissue is a far greater surgical conquest than a presumably good result under an unnecessary scar.

In group C should be included cases of advanced primary lesions and metastases. Though these patients should be given every benefit that surgical intervention and radium therapy can feasibly and practically offer, there is no doubt concerning the prognosis.

The present analysis of cases has been divided into two parts. In part I, the clinical picture is correlated with the pathologic observations

TABLE 1.—*Correlation Between Histologic Appearance of Primary Lesion and the Clinical Course*

1. Only "V" Section		
Case	Follow-Up and Comments	
1	Well, 5 years*	
2	Well, 12 years	
3	Well, 6 years; an adenocarcinoma	
4	Well, 4 years	
5	Well, 2 years	
6	Well, 5 years; small sore on lip at present	
7	Well, 5 years	
8	Well, 5 years, "V" section; removed a gland for biopsy, which was negative; excision of recurrence on lip one month later; now well after five years	
9	Early recurrence on lip, treated elsewhere	
10	Recurrence on lip (4 by 8 cm.) with walnut-sized gland in left submaxilla one year, nine months later; lesion practically inoperable when first seen; plastic repair of lip necessary, and operation palliative	
11	No radical operation because of age; returned in five months with painful mass in right submaxillary region; too advanced for benefit	
12	"V" section with plastic operation; operation only for palliation; no report	
13	No report	
14	No report	
15	Well, 7 years; died of other cause	
16	No report	
17	No report	
18	Had no palpable glands; no report	
19	Well, 8 years	
20	Well, 9 years	
21	Deep ulcer, no palpable glands; required plastic operation; no report	
22	Required plastic operation; no report	
2a. Radical Bilateral Dissection; Clinically, Metastasis; Microscopically, Negative		
Case	Comment	Follow-Up
23	Had small hard submental gland.....	Well 7 years
24	Had small freely movable submaxillary gland.....	Well 9 years
25	Operation, 1921; recurrence (?) ten years later; submaxillary gland removed in 1931; microscopically negative (fig. 1)	
26	.....	Red pimple appears on lip occasionally and goes away; otherwise well three years
27	Bilateral metastasis clinically.....	Well 4 months
28	.....	No report
29	.....	No report
30	.....	No report
31	.....	No report
32	.....	Well 8 years
33	.....	No report
34	Clinical submental carcinoma.....	Well 8 years
35	.....	No report
36	A gland near median line was aberrant thyroid.....	Well 14 years
37	Lip well 11 years; lesion developed on back of tongue destroying one half of tongue and causing aphonia; diagnosed as tuberculosis by home physician	
38	.....	No report
2b. Radical Bilateral Dissection; Clinically, Metastasis; Microscopically, Positive		
Case	Follow-Up	
39	Returned in 2 months (dry mouth), no recurrence; 4 months later, walnut-sized metastasis to left submaxillary; excised; 1 month later, two more metastatic nodules; 2 months later, many cervical nodes involved	
40	Well 3 years	
41	No recurrence in 16 months; swelling in left lower part of neck 3 years later	
42	Recurrence on lip in 2 months and metastasis in right submaxillary region growing fast and painful	
43	Well 2.5 years	
44	Well 10 years (seen in person; result excellent)	
45	Died in 7 months; tumor destroyed lower part of face, tongue and part of upper jaw	
46	Died in 2 years of recurrence	
47	Died in 2 years from extension in the neck	
2c. Radical Bilateral Dissection; Clinically, Negative; Microscopically, Positive		
Case	Comment	Follow-Up
48	No glands mentioned in the record of this patient, but at operation, a left submental metastatic node found which should have been palpated clinically	8 years later "sore" appeared on the lip, disappeared under home remedies; no recurrence for 3 years

\* The follow-up denotes the status to the end of 1930. "Well" means that there is no evidence of any lesion on the lip or palpable lump under the jaws or chin.

TABLE 1.—*Correlation Between Histologic Appearance of Primary Lesion and the Clinical Course—Continued**2d. Radical Bilateral Dissection; Clinically, Negative; Microscopically, Negative*

Case	Follow-Up
49	Well, 2 years
50	Well, 2.5 years
51	Well, 2 years
52	Well, 2 years
53	Well, 2 years
54	Well, 2 years
55	Well, 2.5 years
56	Well, 10 years
57	Well, 5 years
58	Died in 15 months of other cause; lip well
59	No report
60	No report
61	Well, 2 years
62	Well, 3 years

*3. Radical Unilateral Dissection*

Case	Comment	Follow-Up
63	Clinically and microscopically negative; right radical dissection	Well 3 years
64	Clinically and microscopically negative.....	Well until death from other cause
65	Clinically and microscopically negative; left radical dissection	Died in 5 years of other cause; lip well
66	Clinical findings positive for glands on left; microscopically negative	Well 3 years
67	Clinical data positive for submental gland; microscopic data negative	Well 3 years
68	Clinically positive; microscopic data negative.....	Well 3 years
69	Clinical findings suggestive; microscopic data negative; right radical dissection	Died of other cause in 9 years; lip well
70	Clinical findings suggestive; microscopic data negative; left radical dissection	10 years later small sore developed on left lower lip; stated appearance not like cancer
71	Clinical findings suggestive; microscopic data negative; left radical dissection	Well 15 years
72	Clinical findings suggestive; microscopic data negative; left radical dissection	No report
73	Clinical data suggestive; microscopic observations negative; left radical dissection	Well 12 years
74	Clinical and microscopic data positive.....	Died in 8 months of recurrence in neck
75	Clinical and microscopic data positive.....	Recurrence in lip and neck in 10 months
76	Clinical and microscopic data positive; enlarged gland at carotid bifurcation	Well ? years
77	Clinical and microscopic data positive; left radical dissection	No report

on the glands and the subsequent course. In part II, an independent study of the primary lesion is made in an attempt to find a correlation between its histologic features and the course of the disease.

#### I. CORRELATION OF CLINICAL PICTURE WITH PATHOLOGIC OBSERVATIONS

*Analysis of Cases (Table 1).*—The following analysis was made of seventy-seven consecutive cases. They were grouped in three categories:

(1) Cases in which only a "V" section was made for the primary condition and in which the patients were spared the radical operation.

There were twenty-two cases. In eleven the patients have remained well for from four to twelve years; one of them presented a primary

adenocarcinoma of the lip; in two cases the condition was too advanced when the patient was first seen for more than palliation to be attempted, and in eight cases there was no report.

(2) Cases in which bilateral radical dissection of the submaxillary nodes, including the submaxillary salivary glands and submental glands, was performed. These naturally fell into four significant groups with regard to regional metastasis:

(a) Cases in which a clinical diagnosis of metastasis was made but in which the microscopic observations were negative. There were sixteen cases of this type; nine of the patients were well for from three to fourteen years, and there was no report on seven.

(b) Cases in which both the clinical and the microscopic observations were positive. There were nine such cases. Three of the patients are well after two and one-half, three and ten years, and the other six either died of recurrence or have a recurrence at the time of writing.

(c) Cases in which the clinical observations were negative and the microscopic ones positive. There was one case of this type. Palpable glands were not mentioned in the record, but at operation a left submental metastatic node was found which should have been palpated clinically. Eight years later a "sore" appeared on the lip. This disappeared after the use of home remedies and has not recurred for three years.

(d) Cases in which both the clinical and the microscopic observations are negative. There were fourteen of this type; eleven of the patients are well after from two to ten years; no report has been received from two, and one died in fifteen months of another cause.

(3.). A group in which only a unilateral radical dissection was done. There were fifteen cases, and they fell into subgroups in about the same proportion as those in which a bilateral radical operation was performed.

*Comment.*—From these cases, little estimation can be made concerning the added value of irradiation. However, in all cases with proved metastases intensive irradiation was employed. In spite of the combined treatment, the mortality from recurrence was greater than 50 per cent.

In studying the microscopic sections, there is no doubt that a biopsy of the glands palpated would have demonstrated metastases when present, thus eliminating the possibility of an oversight. Experience has shown that the fascia or parenchyma of the salivary glands does not exhibit metastatic cancer cells, except in the most obviously advanced lesions.

*Illustrative Case.*—The following report (table 1, case 25) is of considerable interest with respect to clinical impression.

G. O., an American laborer, white, entered the hospital on March 10, 1931, with a carcinoma (recurrent?) of the lower lip. Ten years previously, a carcinoma of the lip was resected with a simple "V" section, and bilateral radical dissection of the glands was done at this hospital. The wound healed uneventfully. Six years ago the patient noticed that he was snagging his lower lip with a jagged upper incisor. Three months ago a painless ulcer appeared to the right of the old scar.

On examination, a vertical midline scar of the lower lip and a linear scar below each mandible could be seen. An ulcerating, fungating carcinoma occupied practically the entire right half of the lip, including a part of the scar region. The base was indurated. A prominent, firm, fixed gland about 1.5 cm. in diameter was located just below the angle of the right mandible.

It is interesting to speculate on whether the carcinoma was recurrent after such a length of time or whether it was a new and independent lesion. However, there was no doubt that the enlarged gland was involved by metastases. The lesion of the lip was excised with an adequate margin, the closure being aided by a right Dieffenbach plastic procedure, and several days later the gland was removed. The latter was examined carefully microscopically; only inflammatory tissue was revealed.

*Factors of Interest.*—All cases occurred in patients between the ages of 38 and 80, and the relative proportions in the fifth, sixth, seventh and eighth decades were 9, 26, 23 and 19.

The relation of males to females was 76:1.

All patients were of the white race.

The duration of the lesion before the patient came to the hospital ranged from three weeks to twenty years. Between these extremes, ordinary averages do not mean a great deal. Curiously enough, however, in the entire group in which there were nonmetastatic lesions, there was an average duration of twice that of the group in which there were metastatic lesions; this fact indicates that neglect of the lesion or its duration is not so important as the type or grade of malignancy.

*Etiology.*—While it is true that in more than 90 per cent of the instances one can elicit the occasion of irritation and trauma to the lips, no correlation between the irritation and the grade of malignancy is exhibited. In fact, the patient presenting one of the most malignant recurrences seen in group 2 b (case 42) did not smoke, and he remembered no trauma other than the initial lesion. While I believe that irritation and trauma conducive to a long-continued inflammation are most important factors in the etiology of cancer, particularly of the skin, they are only factors and ones about which, taken as a whole, little is known. There are, on the one hand, enough patients presenting carcinoma of the lip who do not smoke and, on the other hand, a large enough population of incessant smokers who never have cancer of the lip to make one look on smoking as a specific cause with considerable reservation.

*Summary.*—1. Eighty per cent of epidermoid carcinomas of the lip are essentially a benign form of neoplasm and are slow to metastasize. The prognosis after conservative surgical intervention in these cases ranges from good to excellent.

2. Ability to determine metastasis clinically is inadequate.

3. There is a relatively small group of lesions which appear clinically to be highly malignant. Metastases develop early, and regardless of radical surgical intervention plus intensive irradiation, 50 per cent of the patients at best may be cured.

## II. PATHOLOGY OF THE PRIMARY LESION AND ITS CORRELATION TO METASTASIS AND PROGNOSIS

*Degree of Malignancy.*—It is of interest to note whether there is a dependable relation between the histologic appearance of the primary carcinoma of the lip and the clinical progress and ultimate prognosis.

Since the time of Virchow, it has been recognized that the degree of malignancy of a neoplasm is inversely proportional, in a general way, to the degree of differentiation which the type cell undergoes. The degree of differentiation itself is manifested by the histologic features of the tumor. Broders and McCarthy have made commendable efforts toward classifying neoplasms in four categories on this basis, with the view to introduce a rational correlation between the histology of the primary tumor and what may be expected of its natural history.

In exceptional instances the rules laid down will not hold, but in general they apply with as great a percentage of accuracy as in the interpretation of any complex biologic phenomenon.

In brief, Broders and McCarthy have placed the neoplasms in which the type cell is undergoing the most advanced differentiation (and which therefore are least malignant) in group 1 and those showing the least evidence of differentiation (and which therefore are the most malignant) in group 4. The remainder of the neoplasms they have placed in the intermediate groups, 2 and 3.

In the application of these principles to carcinoma of the lip, keratinization and pearls, in general, give evidence of the advanced differentiation of the epithelial cell, and signify, as a rule, a carcinoma of relatively low malignancy. Other factors must be taken into consideration, but there seems to be no doubt that an epidermoid carcinoma composed of large papilliform groups of cells in fairly regular formation and undergoing complete differentiation to form large, keratinized pearls is a relatively slow-growing tumor with little propensity for early metastasis. Indeed, many of the large keratinized pearls surrounded by a layer of epithelial cells differentiating from a fairly well



defined basal cell to the ultimate corneum appear not unlike tiny epithelial inclusion cysts. Again, such masses of buried epithelium evoke a considerable foreign body reaction and one often sees, in places, many foreign body giant cells, a thick barrier of leukocytic cells and, further, an attempt to check the progress of the lesion with a wall of scar tissue.

On the other hand, when the cells are present in undifferentiated masses or cords and show abundant mitotic figures, as these types most often do, the grade of malignancy is high, with a tendency toward early metastasis. Therefore, there is no question but that a study of the primary lesion can be of considerable value in augmenting the knowledge one has gained from the clinical study.

*Broders' Classification.*—Broders, in 1920, made an extensive survey of 537 cases of carcinoma of the lip.<sup>5</sup> The following is a brief summary of some of the information.

Pathologic observations in cases in which nodes were removed (449 cases):

(a) No metastases found .....	344 (76.62%)
Metastases found .....	105 (23.38%)

(b) Degree of malignancy:

Grade	Per Cent
1. ....	15.82
2. ....	62.01
3. ....	21.04
4. ....	1.11

(c) Average size of ulcer:

Grade	Cm.
1. ....	1.23
2. ....	2.28
3. ....	3.25
4. ....	1.90

	With Metastasis	Without Metastasis
(d) Average size of ulcer .....	3.74 cm.	2.01 cm.
Average duration .....	3.27 yrs.	2.40 yrs.

Therefore (c) and (d) show that the size of the ulcer is no indication of its degree of malignancy. One is not justified in determining the lesion from its gross appearance. The size and duration of the primary lesion are not, within reasonable limits, indications of the presence or absence of metastases.

5. Broders, A. C.: Squamous Cell Epithelioma of the Lip: A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. 74:656 (March 6) 1920.

## (e) Relation of degree of malignancy to metastasis:

Cases	Grade of Malignancy	Metastasis	No Metastasis
67	1	0	67 (100%)
287	2	39	248
92	3	63	29
3	4	3 (100%)	0

Therefore 79 per cent of the cases fall in groups 1 and 2 and 21 per cent in 3 and 4.

In groups 1 and 2 combined, 11 per cent of the cases show metastasis, and 89 per cent are without metastasis.

In groups 3 and 4 combined, 66 per cent of the cases show metastasis, and 34 per cent are without metastasis.

It would seem, then, that there is ample room for discrimination in dealing with carcinoma of the lip, and that some more rational working plan could and should be established for its treatment.

*Author's Classification.*—My associates and I do not follow Broders' classification exactly, but feel that an adequate working plan can be formulated as follows, and it is on this basis that our primary lesions have been classified:

Group 1, the very benign appearing lesions, including warts, so-called precancerous lesions and epidermoid carcinomas, which would fall in Broders' grade 1 (fig. 2).

Group 2, epidermoid carcinomas which show an advanced degree of differentiation, with more extensive keratinization and pearl formation than in group 1 (fig. 3).

Group 3, a group corresponding to Broders' grade 4, that of the obviously malignant lesion as evidenced by lack of differentiation and the abundance of mitotic figures. An occasional lesion will show keratinization and yet will be placed in this group, for example, one in which keratinization is evident but small in amount or one in which the cells are greatly scattered and dissociated, with multiple tiny pearls. The mere presence of a pearl here and there does not necessarily militate against the lesion's being highly malignant. After all, there are no sharp lines of separation (fig. 4).

The microscopic sections of the primary lesions in the following cases were studied and classified without knowledge as to which cases they belonged. The case numbers were later attached. Sections for all of the cases were unfortunately not available. Sections from cases in which the condition was inoperable when the patient was first seen were not included for obvious reasons. Any malignant lesion if neglected and given time enough will become inoperable, owing to either size or metastasis and, as stated early in the paper, attention is not directed to the cases in which the condition is obviously inoperable

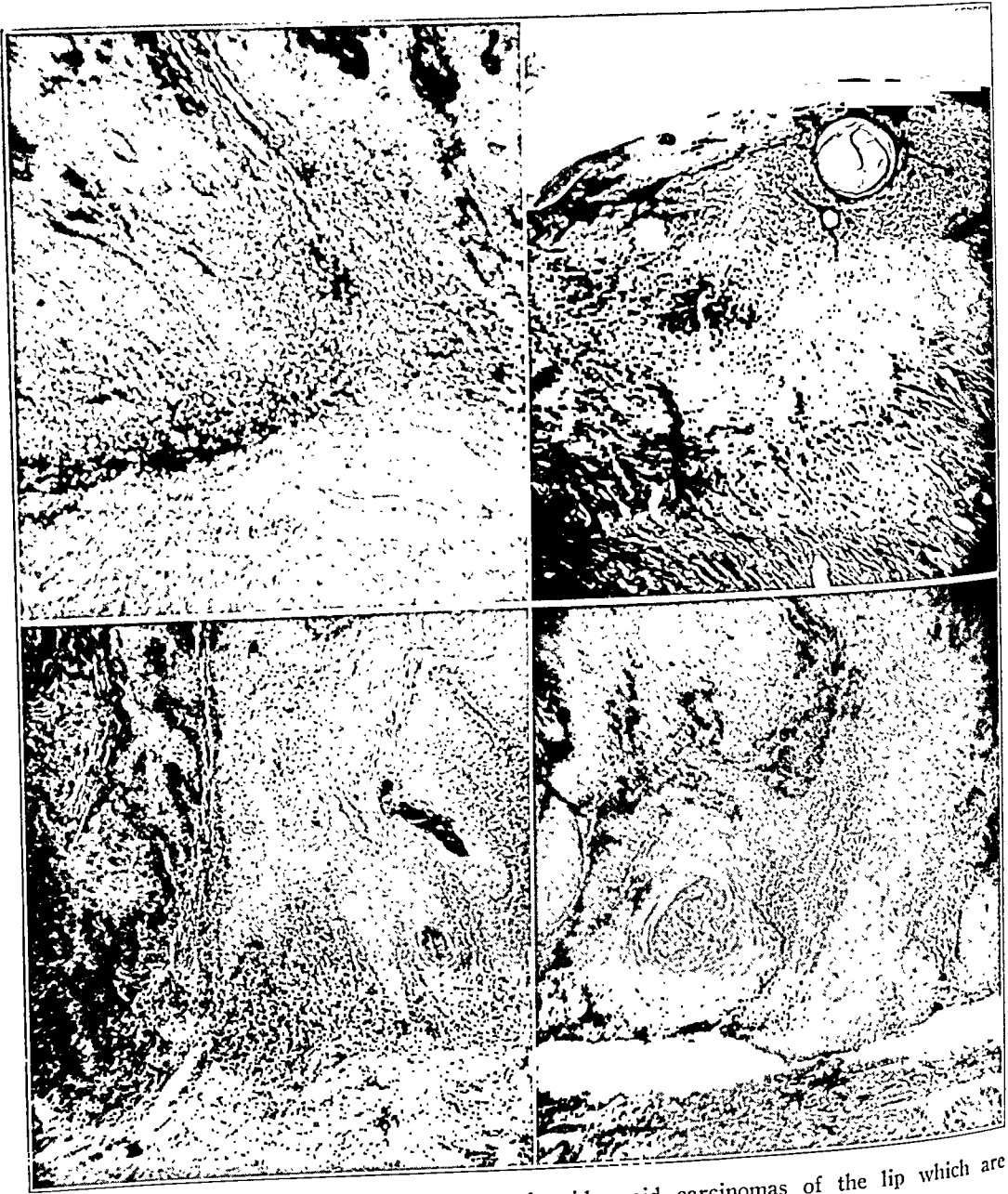


Fig. 2.—Low power photomicrographs of epidermoid carcinomas of the lip which are considered typical of group 1 (table 2).

when first seen. As a corollary to this, occasionally a primary lesion is removed which, though exhibiting the characteristics of high grade malignancy, is not accompanied by metastasis, and a cure will be effected.<sup>6</sup>

*Analysis of Cases (Table 2).*—Sixteen cases fell in group 1. Naturally, all of these lesions showed marked keratinization and well defined limitation. When these were correlated with the respective cases, it was found that a radical dissection of the glands had been performed in twelve. None of these revealed metastases. Ten patients were reported as being well from two to fourteen years afterward.

Twenty cases fell in group 2. All of the lesions showed marked keratinization also, but were not so markedly delimited as in group 1, and

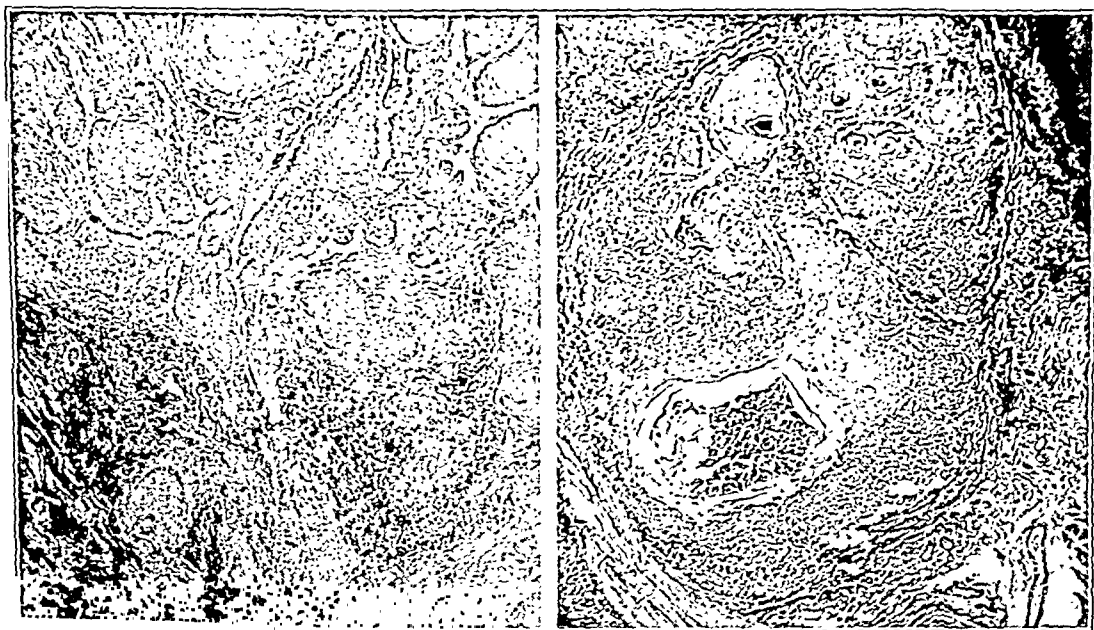


Fig. 3.—Low power photomicrographs of epidermoid carcinomas of the lip which are considered typical of group 2 (table 2).

were more advanced. Twelve patients had undergone the radical operation. Only two of them revealed metastases; in one, the process was fatal, and the other patient has been well for two and one-half years. In eight cases, radical operation was not performed, but five of the patients were reported as being well from five to nine years later.

Ten cases fell in group 3. Seven of the patients had undergone the radical operation; in six instances metastases were revealed. Four of the six patients died with recurrence; one is alive after three years, and the other did not report.

6. Dr. Schenken of the Department of Pathology aided me in the study of the primary lesions.

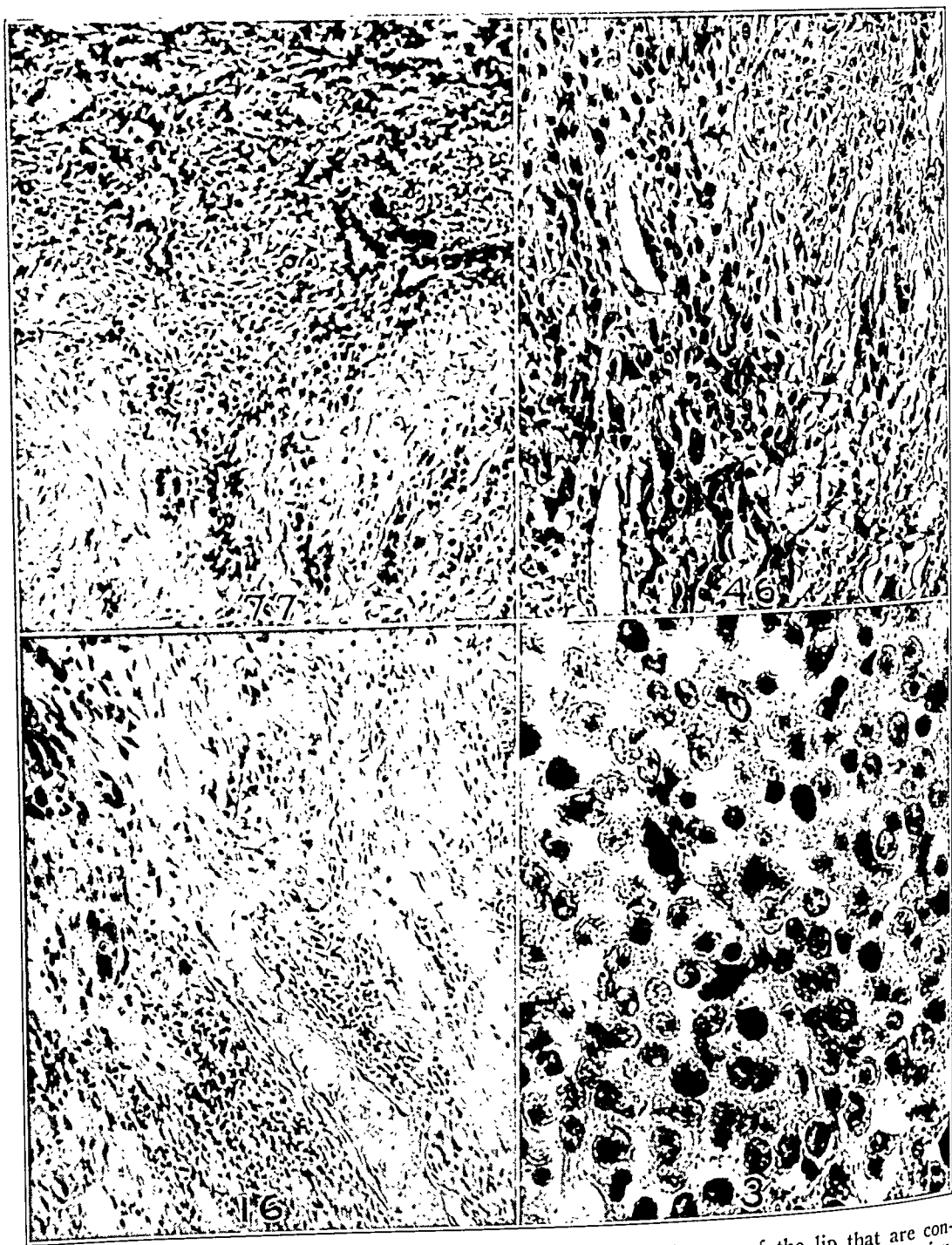


Fig. 4.—High power photomicrographs of epidermoid carcinomas of the lip that are considered typical of group 3 (table 2). These are characterized by little or no keratinization, infiltration and abundant mitotic figures. The photomicrograph from case 3 is an adenocarcinoma of the lower lip, which may well have arisen from a salivary rest, a rare but not unknown carcinoma of the lip.<sup>1</sup> It is included in this group as it should obviously be treated as a highly malignant tumor. Note the many mitotic figures. The primary lesion only was removed in this case, and the patient is well after six years. In the photomicrograph from case 16, a lymph channel is seen filled with cancer cells.

All lesions in this group revealed an undifferentiated cell with infiltration and no keratinization, except one, in which the cells were greatly scattered, and in which there were multiple tiny pearls.

In case 3 the process proved to be a primary adenocarcinoma which appeared highly malignant intrinsically, but which seemed well encapsulated; it was excised with a wide margin. This case is included with the epidermoid carcinomas because when such a process is found it should be obviously treated as a group 3 lesion (case 3, fig. 4).

In summary, therefore, thirty-six of the primary lesions were classed histologically as relatively benign. Only two of them were associated with metastases at the time a radical operation was done. Only a small

TABLE 2.—*Arrangement of Cases According to the Histologic Appearance of the Primary Lesions*

Group 1	Group 2	Group 3
4:K:V:4*	6:K:V:5	16:K:V:—
9:K:V:?	7:K:V:5	3:—:V:6; adenocarcinoma
13:K:V:—	8:K:V:5	54:—:R:N:2
17:K:V:—	14:K:V:—	40:—:R:M:3
23:K:R:N:7	49:K:R:N:2	42:—:R:M: rapid recurrence
26:K:R:N:3	51:K:R:N:2	45:—:R:M: died of recurrence 7 mos.
27:K:R:N:4 mos.	58:K:R:N:—	46:—:R:M: died of recurrence 2 yrs.
28:K:R:N:—	61:K:R:N:2	74:—:R:M: died of recurrence 8 mos.
29:K:R:N:—	67:K:R:N:—	77:—:R:M:—
52:K:R:N:2	18:K:V:—	22:—:VP:—
57:K:R:N:5	34:K:R:N:5	
62:K:R:N:3	19:K:V:5	
63:K:R:N:3	20:K:V:9	
68:K:R:N:3	35:K:R:N:—	
72:K:R:N:—	37:K:R:N:11	
36:K:R:N:14 (aberrant thyroid)	32:K:R:N:5	
	21:K:VP:—	
	31:K:R:N:—	
	39:K:R: microscopic metastasis recurred in many nodes	
	43:K:R: microscopic metastasis, well 2.5 yrs.	

\* Left hand numeral indicates case number; K, keratinization; V, received only "V" section; VP, only "V" section, but required plastic repair; R, some form of radical section; N, no microscopic metastases, and M, demonstrated metastases. The last numeral indicates the number of years the patient has been free from recurrence; and —, no report from follow-up.

percentage remain uprooted as to metastasis, that is, the few patients on whom a radical operation was not performed and from whom a follow-up report was not received. On the other hand, of the ten lesions which were classed as highly malignant histologically, six showed metastases, and more than half ended fatally.

So far as a working knowledge is concerned, one might classify groups 1 and 2 as a single group, except that it is perhaps well to provide a group to accommodate lesions the malignancy of which is questionable. In studying the sections of the primary lesions the impression was gained that the nonkeratinizing ones which fell in the highly malignant class arose from the buccal side of the lip. It seems rather logical that this is true. The usual keratinizing carcinoma of the lip should be comparable to other epidermoid carcinomas of the skin. In general,

the latter are slow-growing, and they metastasize late. On the other hand, carcinomas of the buccal mucous membrane present keratinization less frequently and have a greater propensity for early metastasis as well as for rapid growth.

The results of this review bear out the fact that a rational working plan can be obtained concerning the treatment of carcinoma of the lip with respect to the advisability of a block dissection of the glands of the neck and irradiation. The criteria for formulating judgment as to the method of treatment are: (1) careful clinical examination and (2) microscopic study of the primary lesion. A plan such as the following one may be followed:

(a) If no submaxillary or submental glands are palpable, remove by adequate margin the primary lesion. If the microscopic study proves the lesion to be in groups 1 or 2 as previously mentioned, further surgical intervention would not be advised.

(b) If submaxillary or submental glands are palpable and their condition is questionable, one or more of those most suspected may be easily removed under local anesthesia and examined by the pathologist. Frozen section, if available, may be of considerable aid and expedite further surgical procedures if they are indicated. If the sections do not show metastases, remove the primary lesion only. If microscopic study of the primary lesion proves it to be in groups 1 and 2, further surgical intervention would not be advised. (The glands which were removed may also be studied in the routine manner.) If a metastatic lesion is found in any gland, a thorough bilateral block dissection of at least the submaxillary and submental glands followed by an adequate course of irradiation should be done. (Whether or not block dissection of the anterior cervical nodes should be carried out in such an instance is a matter of personal opinion.)

(c) If the primary lesion falls in group 3, its high grade of malignancy and propensity for early metastasis indicate complete block dissection followed by irradiation, regardless of the clinical findings. If in any instance a patient should be given radical surgical treatment and irradiation, regardless of the clinical findings, it is the patient whose lesion is classified in this group.

It will be observed that irradiation is not advised unless there is surgical intervention. If apparently block dissection of the glands is not indicated, then, to be consistent, irradiation is not indicated. On the other hand, if a metastatic lesion is found, or if the primary lesion falls in group 3, I believe that one should employ both radical surgical treatment and adequate irradiation. When one is dealing with the glands, irradiation is at best only an adjunct to surgical intervention. As a corollary to this statement, I do not feel that unilateral block

dissection of the glands of the neck is ever indicated for carcinoma of the lip. Instances of crossed metastases are too common to make such a procedure adequate.

If the case falls in classification *a*, irradiation alone of the primary lesion may be an alternative procedure, with satisfactory results, but this would deprive one of a study of the lesion, which I feel is of considerably more than academic importance.

*Comment.*—In consideration of the patient's expense for hospitalization, as well as of the problem in charity and in state hospitals where beds are always at a high premium, the question of whether or not a patient should be kept for postoperative irradiation is a constant source of anguish to the surgeon. He often entertains a strong doubt as to either the necessity for or the benefit which may be derived from a course of irradiation in many cases, and yet he wishes to give the patient every benefit that can be had. I feel that this study offers a plan which will dispense with many irregularities. Since block dissection of the glands and irradiation are indicated in a relatively small percentage of cases of carcinoma of the lip, the time of hospitalization for all the patients will be minimum, and yet all the treatment that is indicated will be given. The large group will be spared an unnecessary block dissection of the neck and the small group in which it is indicated will be given the maximum benefit of radical surgical treatment and irradiation.

#### CONCLUSIONS

1. About 80 per cent of epidermoid carcinomas involving not more than one half of the lower lip will not be associated with regional metastases. The indiscriminate use of radical surgical intervention and irradiation is neither necessary nor to the best interest of these patients.

2. A small percentage of carcinomas of the lip are nonkeratinizing and metastasize early. In these cases there are not more than 50 per cent of cures. It is the impression that these lesions arise from the buccal mucous membrane and bear the characteristics of buccal carcinomas elsewhere, while the relatively benign, keratinizing cancer of the lip bears the characteristics of epidermoid carcinomas of the skin in general.

3. One is not licensed to say that epidermoid carcinoma metastasizes early or late without giving consideration to the degree of malignancy in each case.

4. Since for the great majority of patients having carcinoma of the lower lip radical dissection of the glands will be found not to be indicated, these patients should be spared radical operation. On the other hand, when metastasis is proved or when the primary lesion is histo-



logically highly malignant, complete bilateral dissection of the regional glands followed by irradiation should be done.

5. Histologic study of the primary carcinoma is valuable in determining the likelihood of early metastasis.

6. A rational plan for the management of carcinoma of the lip is suggested.

# AMPUTATION THROUGH LOWER THIRD OF LEG FOR DIABETIC AND ARTERIOSCLE- ROTIC GANGRENE

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Frederic S. Dennis,<sup>1</sup> professor of surgery in Bellevue Hospital Medical School, in 1887, during a clinical lecture on the general principles involved in amputation, quoted the late Sir William Fergusson as saying, "Amputation is one of the meanest and yet one of the greatest operations in surgery"—"mean" when resorted to if better may be done and "great" if the only step to give comfort and prolong life.

Probably the earliest amputations done on man precede all available records. However, it is recorded that Hippocrates, 400 years before the Christian era, practiced amputation of gangrenous legs by cutting through the upper portion of the area of gangrene with a chisel and mallet or shears, not entering the sound tissue above the area.

This practice continued until the reign of Augustus Caesar at about the beginning of the Christian era, at which time Celsus was the first to practice circular no flap amputation with a scalpel through sound tissues above the area of gangrene. This technic of Celsus was followed for approximately 1,700 years, until the time of Lowdham of England, who is the first recorded to advocate flap amputations. Alanson,<sup>2</sup> surgeon to the Liverpool Infirmary, published in book form, in 1782, observations of his own and his confreres on the flap method. It was not, however, until the first half of the nineteenth century that flap amputations were universally recognized and practiced. Credit for the advance and improvement of this technic is due to such men as Langenbeck, Lister, Teale, Syme, Lisfranc and Chopart. In 1886, Dennis<sup>1</sup> published his observations on the treatment of amputation by the open method at Bellevue Hospital. He records fourteen consecutive amputations without deaths, performed by Dr. James R. Wood, in which the stumps were left entirely open, as a remarkable surgical achievement at that time.

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Read before the Surgical Section, New York Academy of Medicine, Jan. 8, 1932.

1. Dennis, F. S.: Clinical Lecture on the General Principles Involved in Amputation, *J. A. M. A.* **18**:505 (May 7) 1887.

2. Alanson, E.: Practical Observations on Amputations and the After-Treatment, ed. 2, London, J. Johnson, 1782, p. 8.

Since the discovery of insulin in 1921, and the subsequent study of diabetes and coincident gangrene, amputations in septic diabetes have frequently reverted to the type of operation done by Celsus at the beginning of the Christian era, subsequently known as the guillotine. The so-called guillotine amputation, however, received its name from the technic of Leonard Botalli,<sup>3</sup> surgeon to Charles IX, King of France in the sixteenth century, who first devised and used the guillotine for amputating extremities, sealing the bleeding vessels, immediately after the falling knife had severed the member, with heated irons or oils.

Recent studies of vascular diseases of extremities have brought new problems in amputations, and the development of the technic here reported is an outgrowth of observations during the past two years on patients in the surgical diabetic service of the Presbyterian Hospital.

It is with timidity that I report the following technic as original. The literature on amputations is so extensive that I have not been able to cover it completely, but that which I have reviewed has not produced reference to this type of amputation applied to this group of vascular diseases.

Persons with arteriosclerosis and diabetes constitute a group particularly susceptible to infections and gangrene of their lower extremities. The mortality from amputations in this group is still high in spite of its reduction in various clinics since the introduction of insulin which has permitted more conservative as well as more radical surgical procedures.

The type and site of amputation in cases of arteriosclerotic diabetes demand considerations of the social and economic status of the patient, besides principles of wound healing, routes of infection and the adequacy of the peripheral and collateral circulation. Most persons with diabetes with infected extremities show evidence of advanced general and peripheral sclerosis. Patients with arteriosclerosis and diabetes constitute by far the largest number seen in clinics with infection and gangrene of their lower extremities. The next largest group is composed of those with arteriosclerosis without diabetes and the smallest group of those with diabetes with infection without sclerosis.

The surgical work of Dr. D. F. Jones and Dr. L. McKittrick in conjunction with the medical work of Dr. E. Joslin at the Deaconess Hospital in Boston has recently stimulated the study of surgery in diabetic patients. They have emphasized to the great benefit of septic patients with diabetes and gangrene the efficacy of a guillotine amputation through the lower third of the leg. The immediate effect of this procedure on the condition of sepsis is salutary, if no other septic foci have developed because it separates the patient from the origin of

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3. Watson, B. A.: *Amputations and Their Complications*, Philadelphia, Blakiston's Son & Co., 1885, p. 16.

his infection. They have followed a guillotine amputation, which is a life-saving measure in many cases, by some type of plastic operation on the stump or by higher amputation.

Experience with septic diabetes with gangrene and the success of the guillotine amputation in preventing the continuation or spread of sepsis have established the procedure in the diabetic surgical armamentarium as effective and often dramatic.

Following a guillotine amputation, stumps frequently present the following problem:

1. Slow healing requiring hospitalization for from two to four months, if the patients remain until the wound heals.

To hurry wound healing, Thiersch grafts have been applied to the end of the stump immediately after the amputation. The grafts are maintained in place by soft sea sponges held against them with flamed sterile adhesive strips. These grafts have been observed to "take" on the soft parts, causing earlier complete epithelization. The grafts have been seen in a few cases to "take" over the marrow of the tibia, but in my cases they have not "taken" over the exposed rim of the tibial cortex.

2. Osteomyelitis with sequestration of a portion of the tibia or fibula, usually the tibia.

Retraction of the soft part in spite of adhesive straps attached to the skin with 2 or 3 pound traction cause the tibial end almost as a rule to present at, or distal to, the soft parts. The sequestration of this bone usually requires forty-five days or longer, and healing of the wound is not complete until after sequestration has occurred. This period of healing has been shortened by rongueing off the tibia during the second or third week after the guillotin amputation. This requires no anesthesia.

3. Attachment of the skin to the tibial stump causing pain, and, when an artificial leg is fitted, often ulceration requiring reamputation.

Observations of stumps produced by guillotine amputation, when fitted to artificial legs, the weight being borne by a laced cuff about the thigh and a socket fitting under the tibial condyle and fibular head, have shown that as the stump sinks into the socket, in spite of there being no pressure or weight-bearing on the end, there is a stretching with consequent blanching of the thin epidermal covering of the stump, which in part decreases its blood supply and permits slight trauma to cause ulceration in the scar.

Reamputation after the guillotine procedure prolongs hospitalization and adds physical and mental strain to already debilitated patients with diabetes. Reamputation higher through the leg involves a decided risk of infection in the stump, sepsis and still further, an amputation through the thigh.

Subsequent Gritti-Stokes amputations deprive the patient of his knee joint. A man who does manual labor may be provided with the most useful type of stump, but this has not seemed to have been true of the more sedentary housewife.

An amputation through the thigh, in spite of its success in other clinics, has seemed to the surgical group at the Presbyterian Hospital often more radical than necessary.

Patients with diabetes and sclerosis with compromised myocardium and peripheral vessel walls, decreased kidney function and innumerable other pathologic signs encountered with an early senility do not stand multiple or repeated surgical procedures well. Death has come so frequently, quickly and unexpectedly, and so often has remained unexplained even by autopsy, that in spite of satisfactory clinical records of cardiorenal vascular competency, I feel a guarded prognosis is necessary in all of these cases.

With the foregoing facts in mind, a type of amputation embodying the following principles was sought:

1. The least possible interference with collateral circulation.
2. More rapid healing of the wound.
3. Guillotine amputation of the soft parts at a right angle.
4. A sufficiently well nourished soft part covering of the ends of the bones.
5. Preservation of the knee joint.
6. The least possible shock.

The following technic of amputation through the lower third of the leg which has proved its usefulness in cases of diabetes and arteriosclerosis in the surgical diabetic clinic at the Presbyterian Hospital is herewith presented.

#### OPERATIVE TECHNIC

No tourniquet is used except the assistant's encircling hands. After proper preparation of the skin and draping, an incision is begun from 6 to 7 inches (15.2 to 17.8 cm.) below the tibial tubercle over the medial margin of the anteromedial surface of the tibia, at least 3 cm. medial to the tibial crest, deepened through the skin to the periosteum and extended distally from 4 to 5 inches (10.2 to 12.7 cm.) to the point at which the soft parts will be guillotined (fig. 1).

With a curved periosteal elevator, the medial, posterior and lateral group of muscles are separated from the tibia, outside its periosteum. The curved elevator or a flat flexible retractor is left in place posterior to the tibia (fig. 2).

The tibia is severed from 6 to 7 inches below the tubercle, at the upper end of the skin incision, with a Gigli saw or flat chisel. With the latter, there is added danger of injury to the muscles and vessels. The sclerotic tibia may be difficult to sever with a Gigli saw alone. The severed tibia is forcefully drawn forward and medially out of the wound with a hook or rake retractor (figs. 3, 4 and 5).

To sever the fibula, the extensor group of muscles lateral to the tibia is retracted laterally, exposing the fibula. It is easier technically to expose it about 2 cm. below the level at which the tibia has been severed. The

muscles which take origin from the medial surface of the fibula, namely, the extensor hallucis longus, the extensor digitorum longus and the peroneus tertius, are separated for a short distance from the fibula at this point, and the bone is palpated and severed with bone forceps (fig. 5). Care must be taken lest the ends of the bone forceps extend beyond the fibula laterally or posteriorly and damage the peroneal vessels which lie posterolateral to the shaft of the fibula.

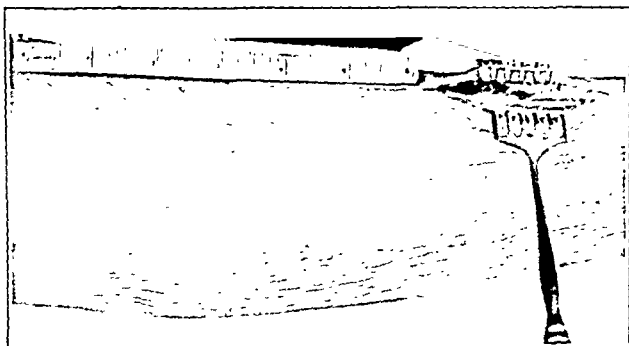


Fig. 1.—The skin is incised down to the periosteum on the anteromedial surface of the tibia from 6 inches below the anterior tibial tubercle to the site chosen for amputation of the soft parts.



Fig. 2.—The tibialis anterior, the extensor digitorum longus, flexor digitorum communis longus and tibialis posterior muscles were separated from the periosteum of the tibia with a curved periosteal elevator.

Both bones in the part to be amputated are then brought forward out of the wound by depressing the foot (figs. 6 and 7).

This enables the operator to see the muscular attachments which have been severed from the tibia and those to be separated from the fibula downward to the point at which the soft parts are to be guillotined. The muscles can easily be separated from the tibia with a periosteal elevator, but from the fibula the peroneus tertius is best separated by curved scissors (fig. 7).

Once the tibia and fibula have been brought forward out of the wound and separated from their investing muscles, an amputation knife is placed posterior to the bones from 4 to 5 inches below the site of their severance, and the soft parts are guillotined at right angles (fig. 8).

It is important that the guillotine incision through the soft part be at a right angle as this destroys fewer collateral vessels than an oblique incision.

The muscles are then separated from the fibula stump which is still longer than the tibia, and it is reamputated with its periosteum from 1 to 2 cm. above the end of the tibia with a bone forceps (figs. 9 and 10). The tibial crest is beveled through its cortex down to, but not into, the medullary cavity. This minimizes skin injury and bone bleeding and prevents the formation of a subcutaneous hematoma at this point. After the vessels are clamped they are ligated without mass ligatures. The posterior tibial nerve is pulled down for 2 or 3 inches (5 to 7.6 cm.)

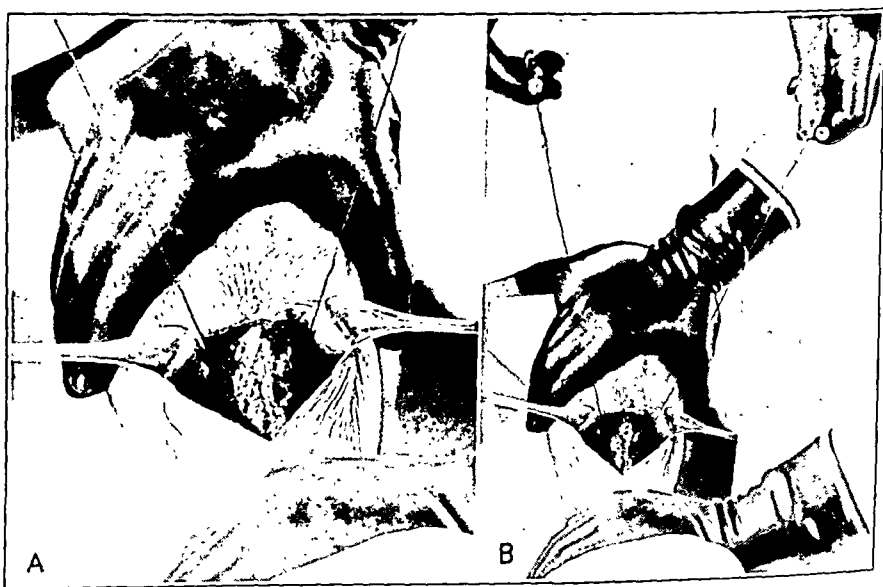


Fig. 3.—*A*, the Gigli saw is in place posterior to the tibia at the upper angle of the wound for division of the tibia. The soft parts are retracted and protected by medium abdominal retractors. *B*, the tibia is being cut across.

and 1 cc. of 1 per cent procaine hydrochloride followed by 1 cc. of 80 per cent alcohol is injected into it; the nerve is severed and allowed to retract.

Closure has been done as follows (fig. 11):

1. Careful hemostasis is employed.
2. In some but not in all cases, the deep fascia is sutured with plain interrupted catgut on a small curved needle, care being taken to approximate the edges exactly.
3. Interrupted silk sutures are used in the skin.

In cases in which drainage is employed skin closure does not approximate the drain too closely.

The soft parts are sutured, drained or left open, depending on the extent of the infection in the foot and tissues through which the amputation is done. When amputation is done for gangrene or infection, the end of the stump is considered a contaminated, potentially infected wound because the lymphatic channels have been divided.

I have employed drainage in all cases in which this method was used to date, a small soft rubber tube or rubber dam being placed down to the space just posterior to the end of the tibia.

Drainage has been used as an added safety factor. The extent and time of drainage have gradually been decreased with added experience in these cases, and although the ultimate aim is for a minimum, I doubt the advisability of closing the stump as a routine procedure without some form of drainage.

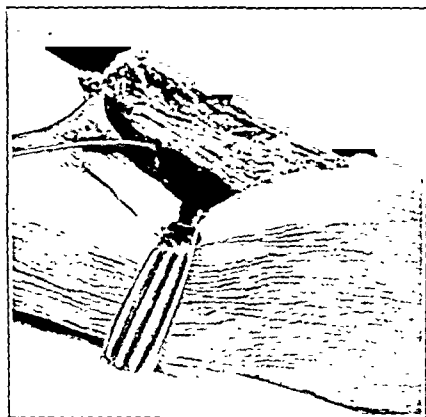


Fig. 4.—The tibia has been cut across and the flexor digitorum communis longus and interosseous membrane have been stripped away from it outside the periosteum with a curved elevator.

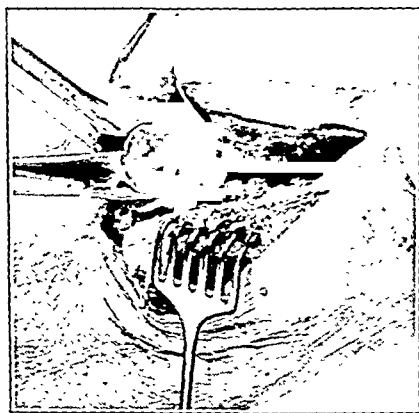


Fig. 5.—The severed lower portion of the tibia is retracted medially. The fibula has been exposed along the interosseous membrane, care being taken to avoid the anterotibial vessels anteriorly, and the peroneal vessels posteriorly near the fibula. The fibula is severed by bone forceps about 2 cm. below the tibia. It is reamputated higher than the tibia later (fig. 9). Exposure of the fibula is technically the most difficult part of this amputation.

Where the limb has been severed through cellulitis and thrombophlebitis, the wound has been left wide open with a small tampon type of a drain of China silk with one or two 1 inch (1.27 cm.) strips of gauze inside the silk. This type of wound is usually converted into an open dressing from about the fourth or fifth



day on. In the partially sutured drained wounds, the tube or rubber dam is usually withdrawn the second day and not replaced unless deemed advisable from the clinical course.

The operator should decide the length of soft parts desired over the ends of the bones. I have found a soft part pad of from  $3\frac{1}{2}$  to 5 inches (8.9 to 12.7 cm.) immediately after amputation to have shrunk to one of from 2 to 3 inches six months later. This has been satisfactory to the patient and also to the makers of



Fig. 6.—The severed fibula and tibial ends are brought out of the wound by depressing the foot, and the muscle groups have been separated from the periosteum of the two bones down to the site at which the soft parts will be amputated.

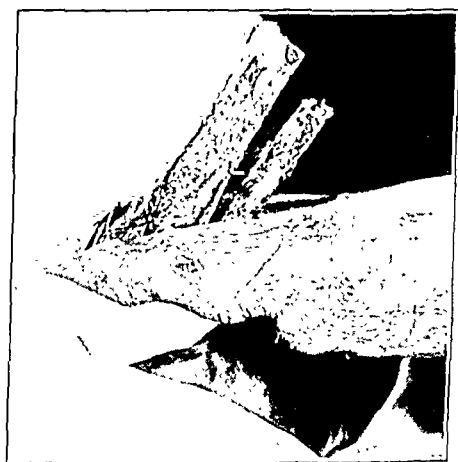


Fig. 7.—Lateral view of figure 6.

artificial legs, because the end of the stump does not extend too far into the socket to require its lower end being wider than the opposite leg at a corresponding level. This is of cosmetic value to the patient and has avoided the difficulty encountered by manufacturers of prosthesis with the long stumps following guillotine amputations through the lower third of the leg.

With this procedure the necessary subsequent plastic operation is done at the time of amputation. Whereas there is more trauma to the tissue than with the

guillotine amputation, there is, however, less than with flap amputations. To sever the tibia between 6 and 7 inches below its tubercle and leave only a small portion of soft parts covering the bones would necessitate amputation through the lower muscle bellies in the middle third rather than through the tendons in the lower third. Fewer tissue spaces are opened and less collateral circulation disturbed by amputation through tendons than through muscle bellies. This obviously promotes better healing and tends to obviate infection. If tendons interfere with closure of the wound, they are excised near their juncture with the muscle bellies.



Fig. 8.—The amputation knife in position at right angle to the soft parts, severing them in the lower third of the leg from 3 to 4 inches below the site of the bone amputation.

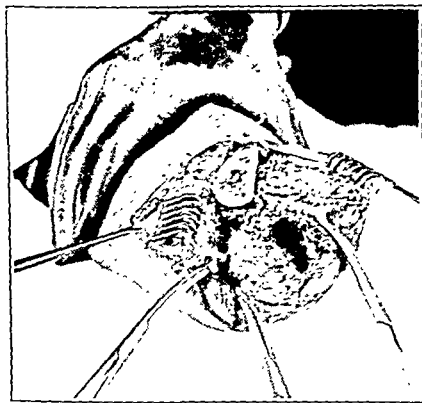


Fig. 9.—End of the amputated stump. The hand was used as a tourniquet. Clamps were placed on the anterior and posterior tibial vessels and posterior tibial nerve, which was pulled down and 1 cc. of 1 per cent procaine hydrochloride followed by 1 cc. of 80 per cent alcohol injected into it. The nerve is divided and allowed to retract.

*Dressings.*—The amputation wound, depending, of course, on the clinical signs of the presence of infection, is not dressed preferably for from twelve to fourteen days. This allows tissue relationships to be undisturbed for such an interval that repair of the wound is sufficiently strong to prevent the stump components from separating. The old dictum of not lifting the stump off the bed or dressing the stump without support posteriorly has been closely followed, as my co-workers

and I have frequently demonstrated that this has prevented the soft parts from opening and falling away from the bones and from each other.

Particular care is taken in dressing the stump at operation. We have used a type of dressing that has consistently proved satisfactory. It is done as follows:

1. A strip of fine meshed gauze soaked in surgical solution of chlorinated soda (Dakin's solution) covers the suture line on each side of the drain.



Fig. 10.—The peroneus tertius, brevis and flexor hallucis longus have been separated from the fibula with curved scissors and retracted. The fibula is reamputated 1 inch above the end of the tibia. The anterior tibial crest is beveled for from  $\frac{1}{2}$  to 1 inch.

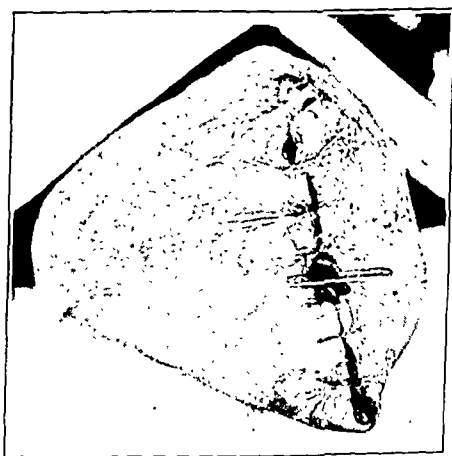


Fig. 11.—The deep fascia has not been sutured. The skin is sutured with interrupted dermal sutures and a rubber dam drain placed down to the dead space below the tibia.

2. Fluffed gauze covers the end of the stump, evenly diffusing the pressure.

3. A flamed mole-skin adhesive strip is placed on the posterior portion of the knee and crural regions partially surrounding the stump for one-half its circumference. The end of this strip distally is cut and folded so that a strip 1 inch wide is made to which by a small rope a 2 to 3 pound (0.9 to 1.4 Kg.) weight for traction can be applied through a pulley fixed to the end of the bed, as soon as the patient is returned to bed.

4. A cushiony pad covered with gauze smeared with ointment of boric acid on its inner surface is placed behind the distal third of the stump, between the adhesive strap and the skin.

5. The entire large dressing is bandaged snugly and evenly with from 2 to 3 five yard rolls.

6. Adhesive strips from 1 to 2 inches wide are placed spirally over the rolls, reaching well up on to the thigh in order to anchor the dressing.

This type of dressing has accomplished the following:

1. Its large size insures comfort and absorption of drainage without external soiling.

2. Even diffusion of pressure insures good tissue approximation.

3. Skin traction maintains the length of the soft parts and overcomes muscle spasm.

4. The stump with its dressing can be moved quite painlessly by using the traction strap as a support.

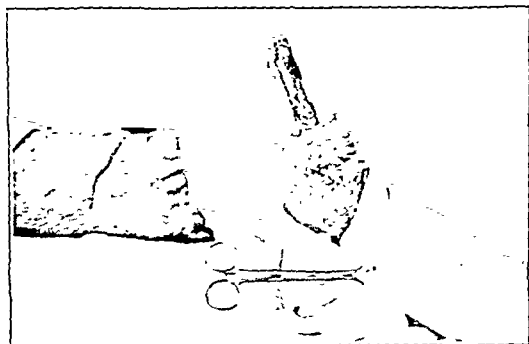


Fig. 12.—Lateral view of the stump. The black line represents the plane of the ends of the bones. The specimen shows the soft parts amputated  $2\frac{3}{4}$  inches below the bones.

5. Motion of the stump within the dressing is not possible. When motion is permitted in the dressing, it has been found to be painful.

6. The dressing is maintained in place for from twelve to fourteen days comfortably.

7. Removal of drains is possible without taking the entire dressing down.

To remove a drain shortly after amputation, before the stump is to be dressed, we have found it useful to tie to the drain a piece of heavy silk string, bringing the end out into the dressing near the surface, yet covering it with gauze, where it can be easily found. By means of this string the drain can be withdrawn from the wound and dressing or from the wound only, leaving it in the large dressing, without disturbing that part of the dressing adjacent to the wound.

Subsequent dressings are done only as indicated. Meticulous care is urged, however, in dressing these stumps wherein infection lurks in the presence of a diminished blood supply.

Healing of the amputation stump is retarded by too frequent dressings. The repair process in these stumps is slow because of the diminished blood supply. Dressings rearrange healing tissue relationships; primary union of tissues in juxtaposition is interfered with when this relationship is changed by an unnecessary

dressing. Bacteria unable to proliferate in these approximated healing tissues may cause active infection following even minimal damage to tissues from manipulation while dressing. The stumps are always dressed with the foregoing facts in mind.

The fundamental principle of this operation is the minimum interference with the collateral blood supply. The amputation of both bones above the site of the severance of the soft parts leaves the ends of the bone well covered for from 3 to 4 inches, and after shrinkage, as seen three, six and twelve months later, there remains a painless movable soft stump for 2 or 3 inches beyond the ends of the bone. The blood supply, both collateral and peripheral, is so well maintained that ulceration such as that seen from stretching trauma about the ends of the true guillotine stumps has not been encountered.

The follow-up has not been sufficiently long to determine whether the incision on the anteromedial surface of the soft parts of the stump will continue to be painless and free from ulceration with weight-bearing on the condyles of the tibia, but cases followed for three and one-half years have not shown such trouble.

However, the follow-up in these cases to date, although relatively short (three and one-half years), has been uniformly good, and sufficient time has elapsed to have allowed a general recovery and stabilization of these patients from the depletion of their amputations.

#### REPORT OF ILLUSTRATIVE CASES

CASE 1.—*History*.—L. M., a Russian woman, aged 40, was admitted to the Presbyterian Hospital on Jan. 7, 1929, complaining of a sore right foot of two weeks' duration. She had lived in New York for eighteen years (fig. 13).

Two weeks before admission she noticed a fissure in the skin between the right first and second toes. This area swelled and became cyanotic, and she consulted her local doctor, who found sugar in her urine. She did not know she had diabetes.

On arrival at the clinic her urine showed dextrose 4 plus and a 4 plus ferric chloride reaction. She had an acetone breath. She had never been on a diet or taken insulin. Her past history was essentially unimportant, except for the following positive facts: All her life she had been a hard working woman. At the time of examination she was supporting three children. For the past three years she had worn glasses for reading. She had never previously been in a hospital. She had never been obese nor had her weight changed. There was no history of skin infection. Her catamenial history was normal.

On admission the temperature was 102 F.; the pulse rate, 120; respiration, 20, and blood pressure, 150 systolic and 90 diastolic. There was no family history of diabetes.

The right foot revealed cellulitis, gangrene and deep cyanosis of the great and second toes. The cellulitis extended up near the junction of the lower and middle thirds of the leg. Wound culture showed hemolytic streptococcus. The blood culture was negative.

The blood sugar was 2.81 Gm. per liter; the blood urea, 0.24 Gm. There were 27,100 white blood cells and 92 per cent polymorphonuclears.

For two days the patient was given a clysis of 1,500 cc. of 5 per cent dextrose with 25 units of insulin, which cleared the diacetic acid from her urine.

She was septic; the temperature was 102 F., and the pulse rate varied from 90 to 120. On the dorsal surface of the foot there was an area of dry gangrene, 8 by 10 cm. Pus discharged copiously from a sinus at the base of the great toe, on the plantar medial surface. There was no lymphangitis extending up the leg and no regional lymphadenitis. The dorsalis pedis and posterior tibial vessels were not felt in either foot. The right popliteal and the femoral vessels were palpable. The lungs and heart were functioning normally, and no pathologic sounds were heard. The radials were beaded.

The patient's collateral circulation was good, as evidenced by a warm skin down to her foot. Dextrose and insulin had reduced the sugar in the urine to 1 plus, and there were no ketogenic bodies in the urine, although the blood sugar was 2.8 Gm. per liter.

*Operation.*—Because of the severe infection and gangrene it was thought safest simply to rid the patient of the gangrenous area by guillotine amputation through the lower third of the leg. Fewer tissue spaces are opened there than when the

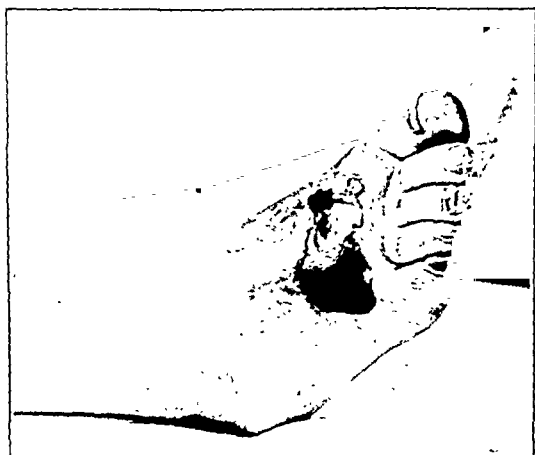


Fig. 13.—Condition of the right foot on admission.

amputation is made through the muscles of the middle or the upper third. A Gritti-Stokes amputation could subsequently be done if necessary. An amputation through the lower one third of the thigh might become necessary because of the degree of arteriosclerosis. The other leg and foot were warm. An infection might develop in the other foot and subsequently necessitate amputation. A bilateral Gritti-Stokes operation is not as useful as a Gritti-Stokes operation on one leg and an amputation leaving a knee joint on the other. She might have enough collateral circulation in the right leg to permit an amputation through the lower third. It was decided to operate immediately under ethylene as soon as permission was obtained.

The second day after admission, under ethylene anesthesia, a circular true guillotine amputation was done through the middle third of the right leg. The main vessels bled in spite of the calcification shown in the roentgenogram (fig. 17). The wound was left wide open. Amputation required eight minutes. Culture of the exudate from the foot at operation grew a nonhemolytic streptococcus and non-hemolytic *Staphylococcus aureus*. Anaerobic culture of the muscles at the site of the amputation showed no growth. Aerobic culture of the muscles grew hemolytic streptococcus and hemolytic staphylococcus.

Roentgenograms of the legs showed calcification in the vessels.

*Pathology Report.*—Gross: The specimen consisted of a foot amputated just above the ankle joint. On the dorsum of the foot, just above the base of the toes, was a rectangular black area measuring 5.5 cm. from side to side. At the lateral side of the foot it was 3.5 cm. wide; at the medial side, 2.5 cm. The surface was black and hard. On section the underlying tissues, especially toward the medial side of the foot, were extremely ragged and necrotic and contained a grayish-brown, semifluid, foul material. On dissecting the foot, the dorsalis pedis artery was found to be small. The wall appeared thickened and the lumen narrow, and in the wall there was a marked deposit of calcium which was more prominent in the upper part of the artery than in the lower. On sectioning the first metatarsal, the bone was found to be hard and white.

Microscopic: Sections through the edge of the blackened area were bordered by a thin tissue. At one end of the section this was markedly thinner than at the other end, where examination revealed the presence of a layer of dense connective tissue immediately beneath the skin, rather thickly infiltrated with polymorphonuclear leukocytes.

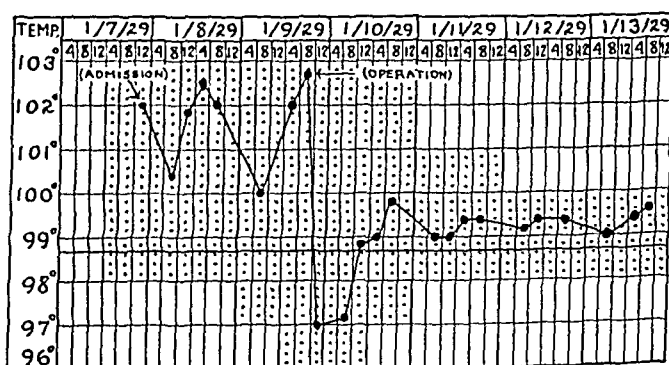


Fig. 14.—Chart showing drop in temperature following guillotine amputation of the right leg.

clear leukocytes and round cells and presenting many small deposits of brownish pigment. There were many lymphatic vessels distended with polymorphonuclear leukocytes. Below this tissue, there was more necrotic tissue thickly packed with polymorphonuclear leukocytes and round cells. In sections from the upper part of the dorsalis pedis, the intima was considerably thickened and contained many large deposits of calcium. In sections from the lower part of the dorsalis pedis, the intima was somewhat thickened, though not as much as in the upper part. The media was thickened and contained several large deposits of calcium. In sections from the first metatarsal, the bone cells were for the most part well preserved. In the marrow cavity, there were many scattered accumulations of polymorphonuclear leukocytes (G. H. Hunt).

The electrocardiogram made January 26 showed the following: sinus rhythm; ventricular rate, 118; P-R interval, 0.14; the P wave, upright in all leads; R<sub>s</sub> notched; S<sub>1</sub> and S<sub>2</sub>, notched; T<sub>1</sub> and T<sub>2</sub>, upright, and T<sub>3</sub>, inverted. The rate was abnormally elevated. Notching of the Q-R-S complex in all three leads suggested slight myocardial involvement (K. B. Turner).

*Course.*—The first dressing was done eleven days after amputation. Up to this time the patient had been exceedingly well. Her temperature dropped dramatically from 102.8 F. to normal the day following amputation and remained normal subse-

quently (fig. 14). Her blood sugar stayed high for a week in spite of large doses of insulin. During the second week, on a diet of 100 Gm. of carbohydrate, 60 of protein and 50 of fat and 40 units of insulin she became sugar-free. The amputation wound showed more granulations in the lower than in the upper half. The ends of the tibia and the fibula were slowly covered by granulations. The wound was rather dry. From the fifteenth day wet dressings were applied in preparation for Thiersch grafts. The skin had retracted from  $\frac{1}{4}$  to  $\frac{1}{2}$  inch (0.63 to 1.27 cm.), and the tissues were flush with the end of the tibia.

Sixteen days after amputation, following extraction of two teeth, the patient had an attack of circulatory collapse, bringing her blood pressure down to 40. There was difficulty in differentiating this from hypoglycemia, and unfortunately the blood sugar was not taken at this time; yet dextrose administered intravenously brought her out of collapse.

On February 8, thirty days after amputation, Thiersch grafts were applied to the stump. Six days after grafting, the stump was dressed and all but two of the grafts had sloughed off. By the second week after grafting, they had prac-

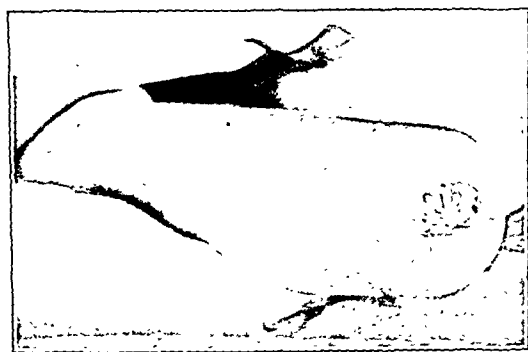


Fig. 15.—End of the guillotined right stump one year after Thiersch grafts had been applied twice. This subsequently had to be revised because of repeated ulcerations on the end of the stump. Revision was done by excising a portion of the tibia and fibula with the same technic as was used in a primary amputation.

tically all sloughed off. Fifty-seven days after amputation, Thiersch grafts were applied the second time. These took well.

On the forty-seventh day after amputation, the tibial cortex which protruded from the wound was rongeuired off. The patient was discharged from the hospital on the seventieth day after amputation. The blood sugar was 1.68 mg. Thirty units of insulin and a diet of 150 Gm. of carbohydrate, 60 of protein and 50 of fat were given. Her urine was sugar-free. When the patient was discharged she was getting 30 units of insulin, the dosage having been decreased from a maximum daily dose of 60 units on admission. The stump was completely epithelized (fig. 15).

Infection about the teeth cleared up following multiple extractions.

*Follow-Up.*—Five months after amputation the skin was adherent to the end of the tibia; there was no pain. The patient had been wearing an artificial leg for one week. The stump was ready for the leg three and a half months after amputation, but it could not be obtained because of financial reasons. The diabetes was under control on a diet of 150 Gm. of carbohydrate, 60 of protein and 100 of fat and 15, 5 and 15 units of insulin.



One year after amputation the right artificial leg was entirely comfortable. The left dorsalis pedis and posterior tibial arteries were not palpable. The patient was referred for prophylactic treatment of the remaining foot.

Eighteen months after amputation, superficial ulceration on the lateral side of the second *left* toe 1 by 1 cm. was noted. An ulcer, 0.25 by 0.5 cm., had appeared on the right stump in the grafted area. The stump measured 25 cm. from the tibial tubercle to its end.

This case illustrates a frequent observation on stumps produced by guillotine operation through the lower one third of the leg; the stump was too long for the best type of prosthesis, and the skin over the tibial end was apt to be traumatized. The patient was wearing her artificial leg in spite of ulceration.

From July to September, 1930, the ulcer on her left second toe failed to respond to treatment at home and by the district nurse, and the patient was readmitted to the



Fig. 16.—Condition of the left foot before amputation.

hospital. The ulcer had existed on the lateral plantar surface of the second left toe for four and one-half months. The patient's temperature was 98.6 F.; the blood pressure, 95 systolic and 80 diastolic. The essential findings were ulceration of the second toe and an ulcer in the amputation stump. Two weeks after admission a small abscess appeared under the nail of the left great toe in spite of all the hospital care. Active hyperemia produced five minutes every two hours with the blood pressure cuff filled to 15 mm. below diastolic pressure on the thigh failed to help the local condition.

*Second Operation.*—On October 4, amputation of the left second toe and revision of the amputation stump of the right leg were done. A roentgenogram failed to show osteomyelitis. Under infiltration anesthesia with 0.5 per cent procaine hydrochloride the ulcer at the end of the right stump was excised and 3 cm. of the tibia and 4 cm. of the fibula was removed with bone forceps. The wound was partially sutured and treated with surgical solution of chlorinated soda; on the

second left toe laterally an ulcer 1 by 0.5 cm. had existed for five months which had not shown evidence of healing under a week of hospital treatment. This toe was amputated under infiltration anesthesia with procaine hydrochloride with a racket incision; the cartilage of the metatarsal joint was removed with a rongeur, and the wound was treated with surgical solution of chlorinated soda. The site of this amputation remained dry and black; ultraconservatism was tried because the patient had had one leg amputated and we were anxious to save the other foot, but it was in vain, and on October 20, sixteen days after amputation of the left second toe, a modified guillotine amputation was done on the left leg at the junction of the lower and middle thirds.

One hundred milligrams of procaine hydrochloride was introduced between the fourth and fifth lumbar vertebrae without difficulty. The anesthesia was complete

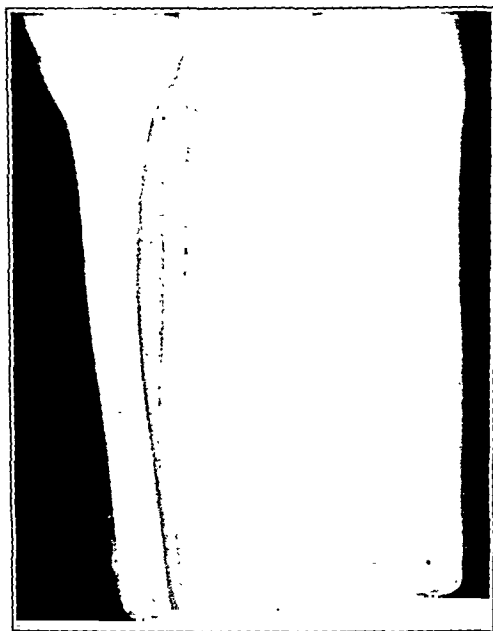


Fig. 17.—Roentgenogram showing calcification of the vessels on the right stump. A similar condition existed on the left.

and satisfactory. An amputation through the lower part of the leg as described in this paper was done. Careful hemostasis was done with fine plain catgut without taking mass ligatures. The posterior tibial artery was a solid calcified cord and bled very little. It was hardly necessary to ligate it. The anterior tibial artery was likewise calcified, but a little more patent than the posterior. The peroneal artery bled. There was little bleeding from the almost eburnated bones. The deep fascia was approximated over the tibial crest anteriorly throughout the wound to within the distal 2 inches. A rubber dam drain was placed down just posteriorly to the site of the amputated tibia. A long silk string was tied to its distal end so it could be removed from the wound without opening the dressing. The skin was closed with dermal sutures. The following note was made by Dr. B. C. Smith:

"The idea of this type of procedure is a modification of guillotine amputation in which the bones are amputated through the upper third of the leg and the soft

parts through the junction of the lower and middle. Whether or not this was a difficult case for the procedure because of the calcified posterior and anterior tibial vessels is hard to say. The patient has very little healing power. This method leaves a good long flap covering the bones distal to their ends. An attempt was made in doing the amputation to open as few tissues as possible; i. e., skin, subcutaneous tissue and muscles were sectioned in the same plane. The muscles were not dissected at all except where they were removed from the bone, thereby not interfering with whatever collateral circulation there has existed."

*Pathology Report.*—Gross: The specimen consisted of the lower left leg cut 32 cm. above the plantar surface of the heel and a piece of white tissue 4 cm. long and 0.5 cm. in width, said to be a piece of the tibial nerve. The amputation showed 10 cm. of bare tibia and fibula above the site of incision. The second toe had been removed, leaving a deep ulcerated cleft between the third and great toe. The ulcer was 1 cm. deep, surrounded by soft necrotic, blackish material with a distinct line limiting this from the more normal tissue proximally. The third toe was bluish, and the ulcerated area extended over to expose the tendon of this toe. The two other toes appeared relatively normal, and there were no other areas of changes in the skin grossly. A complete dissection of the anterior and posterior arteries was done following down the dorsalis pedis, including the ramifications of the digital arteries where they became lost in the ulcerated area. The vessels were alike in consistency, being very brittle, entirely without elasticity, considerably thickened and containing a great deal of hard, gritty, calcium deposits.

*Microscopic:* A section through the margin of the ulcer showed a fairly definite line of demarcation between the relatively normal epithelium proximally and the sequestered structureless epidermis distally. Beneath the skin the line was not so sharply defined. The subcutaneous tissue was infiltrated sparsely with polymorphonuclear leukocytes for some distance proximally and distally became more dense until there was a zone of indistinguishable necrotic material. There was also considerable perivascular infiltration about the small thickened vessels.

Sections of the arteries showed a marked degree of arteriosclerosis, with the greatest changes in the larger vessels. In the upper portion of the posterior tibial artery the lumen was entirely filled with an organized thrombus with little effort at recanalization. It contained a moderate amount of productive, slightly inflammatory granulation tissue in the subintimal layer, and beyond this and extending into the media there was an entire layer of calcification, which in some places had undergone ossification. The musculature of the media was almost entirely replaced by connective tissue, and there was also considerable fibrosis of the adventitia. The lumen in the lower part was very much narrowed but was not thrombosed so that collateral vessels must have been present. All the other vessels showed calcification and considerable fibrosis. The lumen of the dorsalis pedis contained a recent thrombus which had no evidence of beginning organization (Dr. C. J. Kraissl).

Amputation was necessitated by evidences of maintained infection at the site of amputation of the second left toe, which six days after operation was black and dry. Amputation was done by the modified guillotine technic sixteen days after amputation of the toe.

The temperature dropped to normal by the sixth day after amputation of the left leg and continued there. The blood sugar rose to 2 Gm. per liter with the patient on from 40 to 45 units of insulin and a diet of 150 Gm. of carbohydrate, 80 of protein and 100 of fat. Her blood sugar had decreased to 1.17 Gm. per liter thirty-three days after amputation.

The first dressing was done on the tenth day and the sutures were removed on the thirteenth day. On the seventeenth day a slight separation of the edges of the skin occurred. On the twenty-fourth day the edges of the skin had separated more, and there was a granulating area 1 cm. wide in the lower two thirds of the wound. The right stump had completely epithelized.

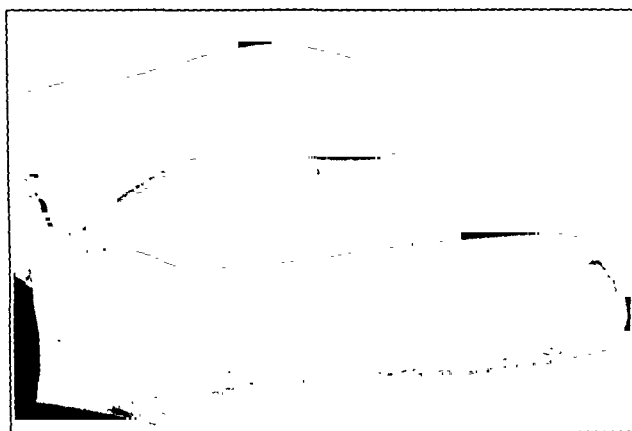


Fig. 18.—Amputation stumps two and one-half years after guillotine amputation of the right stump and ten months after amputation of the left stump by foregoing technic. Note the difference in the length of the parts covering the two stumps.



Fig. 19.—End view of the left amputation stump (author's technic).

On discharge, she was on 8 units of insulin; she had required 45 during her stay in the hospital. A diet of 100 Gm. of carbohydrate, 60 of protein and 50 of fat was given. The blood sugar was 1.17 mg. The urine was normal.

*Follow-Up.*—Eleven months after amputation of the right leg and two months after amputation of the left, both stumps were healed and painless. The patient was walking with an artificial right leg and a crutch, and was to secure the artificial left leg.

Fourteen months after amputation of the right leg and five months after amputation of the left, the right bone stump was 21 cm. long from the tibial tubercle to the end of the soft parts (true guillotine amputation). The left bone stump was 9 cm. from the tibial tubercle and was covered by a 4 inch pad of soft parts. She was wearing two artificial legs and was able to do about 30 per cent of her housework. The results for the right leg were 75 per cent normal anatomically, 100 per cent symptomatically and economically; the results for the left leg were 100 per cent in all three respects.

On July 28, 1931, eighteen months after true guillotine amputation of the right leg and eight months after modified guillotine amputation of the left leg, the patient stated that she liked the artificial left leg better, but I believe this is due to the stump (figs. 18 and 19). There are no ulcers or any pain. She walks with a cane a distance of one-half block. Her result was 100 per cent anatomically,

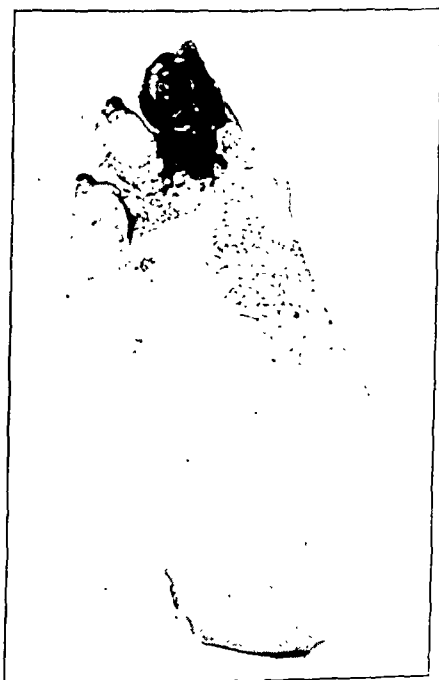


Fig. 20.—Condition of the left foot on admission.

symptomatically and economically for both legs. The blood sugar was 1.51 Gm. The diet was 100 Gm. of carbohydrate, 60 of protein and 50 of fat. The urine was normal.

Ophthalmologic examination revealed diabetic retinitis, retinitis proliferans, arteriosclerosis (marked) and detachment of the retina of the left eye.

On Jan. 8, 1932, two years after guillotine amputation of the right leg through the lower third and fourteen months after revision of the right, true guillotine stump, the patient walked with two artificial legs, doing her housework, and walked as far as three blocks a day outdoors without stopping. The left stump was the most comfortable one. The right has remained healed after the revision.

CASE 2.—*History*.—R. L., a Jewish woman, aged 68, was admitted to Presbyterian Hospital on July 22, 1930, complaining of pain in her second left toe and periods of discoloration with diminished sensation of the left toe for three years (fig. 20).

Three years before admission, while walking, her left foot suddenly became numb and painful. Up to this time she had noticed nothing wrong with her foot. She did not consult her doctor. Two months later a chiropodist pared a corn on her left third toe; it became so painful that she went to a doctor who incised it and found pus. This toe did not heal. Shortly thereafter the left, second and great toes began to change color. She treated them herself with mercurochrome-220 soluble. In spite of physical therapy which she received at a hospital, the great toe became more discolored. No active treatment was given for one year, at the end of which time the fourth toe dropped off. The remaining toes were gradually blackened. During this period she walked on her feet about her housework, but she was unable to walk for four months before admission. The family history did not reveal diabetes. Her best weight twelve years before admission was 172 pounds (78 Kg.). Her weight on admission was 95 pounds (43.1 Kg.).

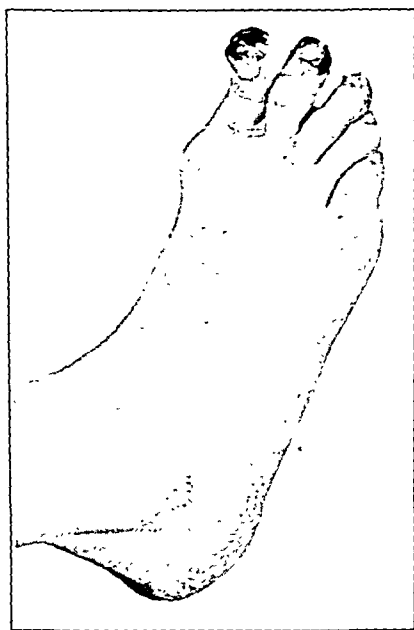


Fig. 21.—Condition of the right foot before amputation.

*Examination.*—Physical examination revealed a rather thin woman of 68, who was not suffering from much pain. The important positive findings were: She had large tonsils not in an acute condition. The lungs were normal. The heart was regular, no enlargement made out, and there were no murmurs. The wall of the abdomen was flaccid and a scar from an operation in the lower left median area had healed firmly. The blood pressure was 186 systolic and 85 diastolic. Her local condition was one of gangrene of the left first, second and third toes. The fourth toe had been spontaneously amputated, and there were cellulitis and edema of the dorsum of the foot. There was pink discoloration of the skin of the distal two thirds of the whole of the foot. The dorsalis pedis and posterior tibial arteries were not palpable in either foot. Both popliteal and femoral arteries were palpable, but the pulsations were less than normal. The patient did not know she had diabetes. On admission the blood sugar was 1.78 Gm., the carbon dioxide-combining power of the plasma was 58 per cent by volume, and the urine showed 2 plus dextrose. The foot emitted a foul odor.

*Operation.*—The day following her admission, under spinal anesthesia (1 cc. of a proprietary procaine preparation in the fourth lumbar space), a circular flap amputation was done by Dr. R. Moore through the lower third of the left leg 4 inches above the malleoli, both bones being amputated 3 inches higher than the soft parts. Injection was not made into the nerves. The tissue cultures of the vessels at operation which did not bleed were negative. Two catheters were placed in each angle of the wound down to the site of the amputated bones for drainage and surgical solution of chlorinated soda was used.

*Pathology Report.*—Gross: There was dry gangrene on the great toe; black dry gangrene on the second toe and gangrene on the plantar surface of the third toe. The skin on the distal two thirds of the dorsal and plantar surfaces of the foot was macerated. The fourth toe had been amputated. The fifth toe was not discolored.

*Microscopic:* On section of the anterior tibial artery the lumen was found to be markedly narrowed by a process of fibrosis in the intima and media. The veins

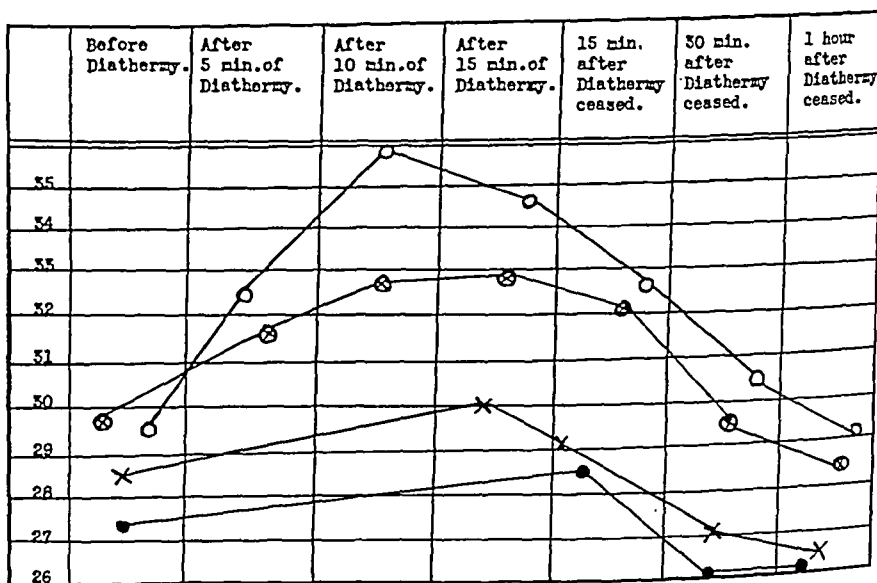


Fig. 22.—Chart of temperature changes of the right leg with and following 200 milliamperes of diathermy for fifteen minutes. The changes in the great toe are indicated by the solid circle; in the fifth toe, by the open circle; in the heel, by the cross and in the dorsum of the foot, by the crossed circle. The room temperature was 71 F.; the mouth temperature, 98.8 F. At 9:48, the toes were warm and tingled.

also showed intimal thickening. The posterior tibial artery was entirely occluded and consisted of simply a fibrous cord, in the wall of which was a piece of bone. The dorsalis pedis shared in the same process but contained a small lumen and also had a piece of bone in the media. The veins here were also thickened.

Section through the tissues around the base of the great toe showed them to be necrotic, especially on the plantar surface, where there was a denser infiltration with polymorphonuclear leukocytes. Aggregations of leukocytes were also seen in the dorsum but were less marked and located chiefly around the vessels near the bone. Several of the vessels contained thrombi which were undergoing organization. The others contained masses of leukocytes.

*Course.*—The diet before operation was 100 Gm. of carbohydrate, 60 of protein and 50 of fat with 10 units of insulin. The day following operation 40 units of

insulin and 125 Gm. of carbohydrate were given, and the blood sugar dropped to 1.09 Gm. per liter.

Spinal anesthesia has not been found to affect the blood sugar in diabetes.

During the remainder of her hospital stay, the patient required only 6 units of insulin daily for two weeks. Her diet was raised to 150 Gm. of carbohydrate, 60 of protein and 100 of fat, and she required no insulin. Her blood sugar was 1 Gm. per liter on discharge. She had essentially arteriosclerotic dry gangrene with mild diabetes.

Following amputation, her temperature rose to 101.6 F., reaching normal in three days, and stayed so during her stay of sixty-seven days in the hospital.

A roentgenogram of the foot before operation showed calcification of the dorsalis pedis and arterial branches of the toes. There was no evidence of osteoporosis or osteomyelitis.

*Follow-Up.*—Three months after amputation of the left leg the tibia was 16 cm. from the tubercle to the end of the stump. The circumference of the stump was 21 cm. at the tibial end. A goodly amount of the soft parts covered the bone and

TABLE 1.—Results of Whirlpool Bath\*

	Left Leg Bath							1 Hr.	2 Hr.
	Before Bath	for 15 Min.	5 Min. After	10 Min.	15 Min.	20 Min.	30 Min.		
Great toe.....	25.0	34.7	33.1	32.4	32.0	32.0	31.7	20.7	26.9
Fifth toe.....	26.0	34.3	33.4	33.0	32.4	32.0	31.6	20.6	26.8
Heel.....	28.0	34.3	34.4	34.2	34.0	33.8	33.8	33.5	30.9
Dorsum.....	30.4	35.4	34.3	34.0	33.8	33.8	33.6	32.7	30.4
Lower one third leg.....	28.4	35.5	34.9	34.3	33.4	33.6	33.6	31.9	30.4
Lower one third thigh.....	29.8	30.9	30.1	31.0	31.0	31.4	31.3	32.1	30.9
Mouth temperature.....		98.4							98.4

\* The temperature with the exception of mouth temperature is given in centigrade.

extended 3 inches beyond it. The patient was ready for an artificial leg. A prosthesis made by the Institute for Crippled and Disabled was being worn four months after amputation.

In nine months slightly reddened areas appeared at the site of weight-bearing in the cuff. This was satisfactorily adjusted. The patient complained of pain in her right foot at this time which showed no change since the previous examination.

In February, 1931, she showed areas of necrosis on the medial side of the distal end of the right great toe and the distal end of the right second toe. The foot was warm, and there was no obvious cellulitis about the areas of necrosis. The pain in the foot was exquisite.

On March 10, 1931, there was an area of gangrene on the right great toe and cellulitis of the second toe. The surface temperatures of the right foot were practically normal, which in the presence of areas of gangrene indicated a fairly active superficial collateral circulation (fig. 21).

The surface temperatures after diathermy were compared with surface temperatures taken after a whirlpool bath, the lower two thirds of the leg being immersed in water at 104 F. for thirty minutes. The results are shown in figure 22.

The amount of rise in the surface temperature after from fifteen to thirty minutes in a whirlpool bath at 110 F. is shown in table 1. The bath was started at 10:15 a. m. with a water temperature of 106 F.

*Operation.*—On March 27, 1931, under gas oxygen anesthesia, amputation through the lower third of the right leg was done by my method for arteriosclerotic





Fig. 23.—Roentgenogram of the right amputated lower third of the leg after injection of 15 per cent bismuth oxide chloride under 20 pounds of pressure, showing a small amount of collateral circulation and no visible main peripheral vessel.

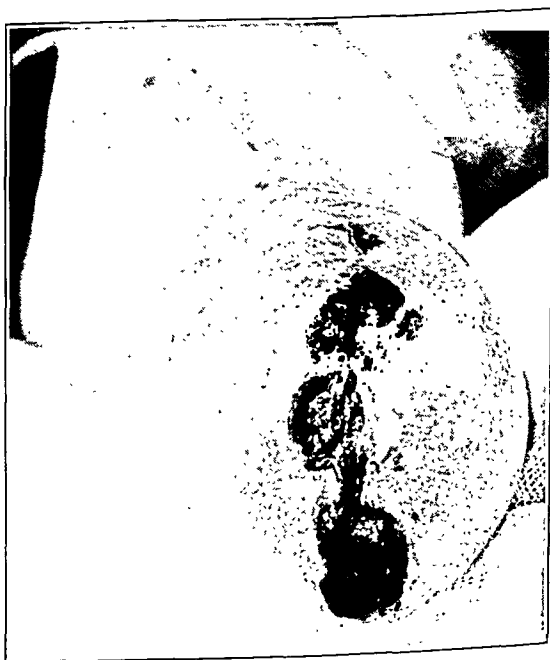


Fig. 24.—Superficial skin slough on the right stump twenty-eight days after amputation.

gangrene of the right great, second and third toes. The posterior tibial vessel did not bleed, but the posterior interosseous and anterior tibial arteries spurted. Bleeding vessels and points in the cut muscles were ligated, care being taken that mass ligatures were not used. The skin was approximated with interrupted dermal sutures, between which in the middle of the suture line a silk drain was placed down to the tibia.

During this second admission the blood sugar varied between 1 and 1.6 Gm. per liter. The patient was discharged on the thirty-first day after amputation with the wound healed. She required no insulin on a diet of 100 Gm. of carbohydrate, 60 of protein and 50 of fat. A roentgenogram before operation showed calcification of the vessels of the leg and toes, dorsum and plantar surface of foot.

*Follow-Up.*—Ten months after amputation of the left leg, the artificial leg still irritated the stump at the site of weight-bearing on the cuff. This was apparently due to the inability to have it adjusted because of hospitalization with the second amputation.

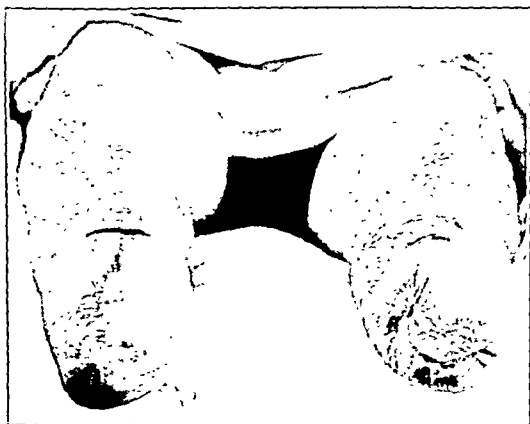


Fig. 25.—Right stump eleven months and left stump nine months after amputation. The right stump shows a small area of necrosis from which a piece of tendon was removed. This area healed in a week.

On June 30, three months after amputation of the right leg, there appeared a small piece of sloughing tendon at the lower angle of the soft part stump. This sloughed away and epithelized following a week of treatment in the hospital.

On July 8, 1931, four months after amputation, the patient wore an artificial leg on the left stump but was not able to purchase the right artificial leg. Her general condition was excellent, and she has a remarkable attitude toward her problem (fig. 25).

On Jan. 8, 1932, ten months after amputation of the right leg and eighteen months after amputation of the left, both stumps were firmly healed and painless. The patient walked about the house with two artificial legs with the aid of a cane. There was a long soft part stump covering the end of the right stump which was amputated by the modified guillotine technic, and this was more comfortable than the left leg where there was a similar pad of the small part covering the ends of the bone.

Two years after the amputation of the right leg she comfortably wore both artificial legs. The right stump was the more comfortable. She walked one or two blocks without the aid of a cane.

CASE 3.—*History*.—D. I., a Jewish woman of 69, complaining of gangrene of the right and left great toe of three months' duration, was admitted to the Presbyterian Hospital on Jan. 26, 1931. The family history did not reveal any diabetes. She was known to have had diabetes for six years. Glycosuria was discovered following a complaint of pruritis vulvae to her local doctor. At this time, in 1925, the glycosuria cleared on a diet. The urine had been tested repeatedly during the last six years and found to be normal. For the past three years she had had cold toes and cramps in her right calf on walking from two to three blocks; these were relieved by resting for from three to five minutes.

Four months previously she noticed a blue spot on her right great toe. Soon afterward a similar area appeared on her left great toe. The blue spot on the right gradually involved the whole toe and similar splotches appeared on the other



Fig. 26.—The right foot on admission showing gangrene, for which the leg was amputated by my technic through the lower third.

toes. Soon afterward, black areas appeared in the skin on the dorsum of the right foot. She had put off medical care because of fear of amputation.

*Examination*.—On admission she was in great pain. Physical examination revealed the following relevant findings (fig. 26): The patient was a well developed and well nourished woman of 69, weighing 133 pounds (60.3 Kg.). She was 5 feet (152.4 cm.) tall. The blood pressure was 160 systolic and 74 diastolic. There was moderate arcus senilis. On percussion the left border of the heart was found 12 cm. from the midline in the fifth space to the left. The apical systolic murmur was transmitted into the axilla. A rough systolic murmur was heard over the aortic site. The lungs were normal. The abdomen was obese. The liver was felt at the costal margin. The radial and brachial arteries were hardened. The popliteal arteries were palpable in both legs. The dorsalis pedis and posterior tibial arteries were not palpable in either extremity. Pelvic and rectal examination gave negative results.

Before operation culture from the gangrenous great toe grew a nonhemolytic streptococcus, *Staphylococcus albus* and *B. coli-communior*.

On January 29, the lateral side of the fourth right toe presented a foul sloughing area 2 by 2 cm., communicating with a sinus in the fourth web, going into the lumbrical canal. The line of demarcation of the great toe was slightly moist. There was a cellulitic blush over the skin of the plantar distal third of the foot. No lymphangitis was present. There was less cellulitis about the areas on the dorsum of the foot. The blood sugar was 1.13 Gm. per liter. The urine was normal. The patient now required a sedative for the pain. The phenolphthalein test was 35 per cent. The temperature was 101 F. There were 4,400,000 red blood cells, 90 per cent hemoglobin, 8,000 white blood cells and 72 per cent polymorphonuclears. Amputation was advised as the infection was threatening and any operation locally would probably only accelerate and not cure it.

The surface temperatures on January 29 are shown in table 2.

The temperatures in table 2 are normal and represent a generous superficial collateral circulation. This is often noted in this type of gangrene, in spite of which sufficient blood supply does not exist for viability of the extremity.

TABLE 2.—*Surface Temperatures Read with a Tycos Dermatherm\**

	Right	Left
Great toe.....	Dry gangrene	30.2
Second toe.....	Ulcerated	30.2
Third toe.....	31.4	30.7
Fourth toe.....	31.4	30.9
Fifth toe.....	31.4	30.4
Dorsum of foot.....	Black necrotic area, 32.4	31.4
Ball.....	31.4	31.7
Concavity.....	31.4	31.7
Heel.....	31.4	31.7
Lower one third of leg.....	31.8	31.8
Middle one third of leg.....	32.4	32.8
Upper one third of leg.....	33.2	32.2
Lower one third of thigh.....	33.0	33.9
Middle one third of thigh.....	33.0	33.9
Mouth temperature.....		98.6 F.
Room temperature.....		74.0 F.

\* The temperature, except room and mouth temperatures, is given in centigrade.

The effect of diathermy on the surface temperatures of her remaining left foot was studied as follows:

The toes were covered with saline-soaked gauze and an electrode bandaged placed over this. The other electrode was placed as a cuff just below the knee and 200 milliamperes of current was run through the electrodes for fifteen minutes. Three minutes after diathermy was begun, the patient stated she had a sensation of slight warmth in her leg.

On January 27, a roentgenogram of the legs and feet showed diffuse calcification of all the vessel walls, more marked in the smaller vessels, suggesting generalized arteriosclerosis. The joints of the feet showed evidence of osteo-arthritis. There were numerous semicalcified, rounded shadows lying in the superficial tissues just anterior to the tibiae suggesting calcified phleboliths.

*Operation.*—On January 30, a modified guillotine amputation through the lower third of the right leg was done, gas and oxygen anesthetic being used. The duration of the operation was twenty-seven minutes. There was a little bleeding from the anterior tibial artery which was partially calcified and a little from the posterior tibial. There was a spurter in the posterior tibial nerve. The nerve was pulled down for 2 inches and procaine hydrochloride with 1 cc. of 95 per cent alcohol injected

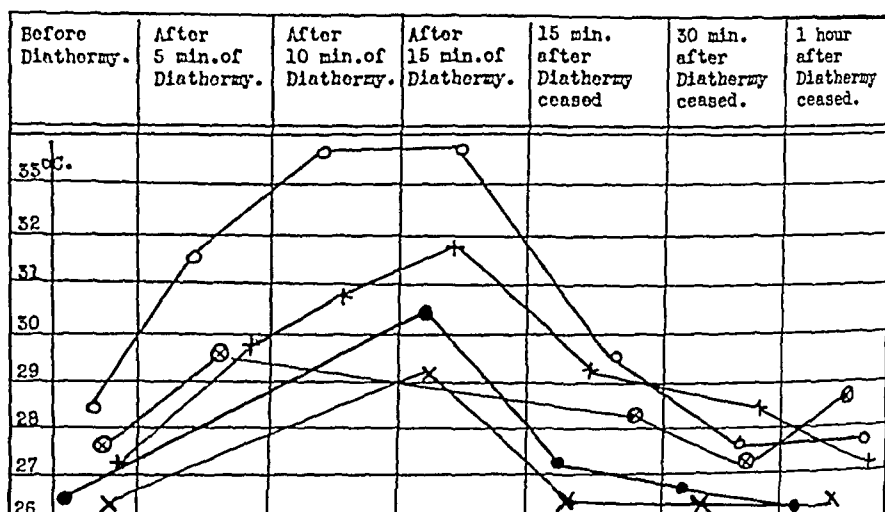


Fig. 27.—Chart of temperature changes in the left leg before and following diathermy of 200 milliamperes for fifteen minutes. One electrode was placed over the toes and the other below the leg. The room temperature was 74 F.; the mouth temperature, 98.6 F. The changes in the various parts are indicated as follows: the dorsum of the foot, the circle; the lower one third of the leg, a plus sign; the heel, a crossed circle; the great toe, a solid circle, and the fifth toe, a times sign.



Fig. 28.—Right stump seventy-four days after amputation showing superficial skin necrosis on the suture line. This was completely healed two weeks later.

into it. The vessel in the nerve had to be ligated. The anterior and posterior tibial artery and vein were ligated separately. There were no mass ligatures used. The tendons of the peroneal muscles were cut away. The skin was sutured with interrupted dermal sutures, and a small tampon drain with silk on the outside, one strip of iodoform and one strip of plain gauze were placed in the space anterior to the soleus muscle at the end of the tibia, because of oozing from the bone and the fact that the lymphatics through this region were probably infected. Dressing was put on with posterior adhesive strap to the skin for traction extending up to the knee. (Dr. B. C. Smith.)

*Course.*—Following amputation, the blood sugar rose to 1.73 Gm. per liter and a plus-minus glycosuria existed for a week. This was controlled by 3 units of insulin for six weeks. On discharge, seventy-nine days after amputation, the patient was sugar-free. The blood sugar was normal, and insulin was not being given.

The amputation wound was first dressed on the third day and a slight discoloration of the skin of the suture line was noted. A portion of the Mikulicz drain was removed. Culture of the amputation stump at this time grew hemolytic *Staphylococcus aureus* and hemolytic *B. subtilis*. The patient developed a small sacral decubitus, which healed with nursing care. Acute conjunctivitis developed twenty-four days after operation. By the twenty-fourth day the skin of the end of the stump had sloughed away for from 1 to 2 cm. on each side of the suture line. A granulating surface there prolonged complete healing of the wound. Collateral circulation of the skin at the amputation site was not sufficient to keep it viable following the injury associated with trauma of amputation.

The patient had rather severe cerebral sclerosis and remained rather disoriented and depressed for about three weeks after operation. The amputation stump epithelized slowly at the site of the skin slough in the suture line, but it completely healed by the seventy-ninth day. She remained in the hospital seventy-nine days because of her debility and mental lack of attempt to help herself to get well.

*Follow-Up.*—The patient began wearing an artificial leg eight months after amputation. This delay was due to infection in her other foot keeping her in a chair. The stump was ready for the prosthesis three months after amputation. The stump has been painless. No ulcerations have occurred, and she has now walked with her artificial leg for four months.

*NOTE.*—June 20, 1933: For three and one half years following amputation of the right leg, the stump has remained symptomless. The patient has worn her artificial leg for three years. She is now in Presbyterian Hospital with gangrene of the remaining foot, and amputation by the same technic will be performed as soon as she grants permission.

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# EFFECT OF MORPHINE ON THE MOVEMENTS OF THE SMALL INTESTINE AND SPHINCTER MUSCLES

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It is generally believed among physicians today that the effect of morphine on the intestine in the doses commonly used is to stop peristalsis and put the bowel at rest. This belief may be due to the results obtained in earlier experiments on isolated intestinal segments, on anesthetized animals or with improper doses of morphine. In the light of recent work it appears quite evident that the effect of morphine on the intestine is one of stimulation and not one of paralysis.

Those who have found paralysis of the small intestine after the administration of morphine are Legros and Onimus,<sup>1</sup> Nothnagel,<sup>2</sup> Leubuscher,<sup>3</sup> Katsch,<sup>4</sup> Meissner,<sup>5</sup> Zunz and Gyorgy,<sup>6</sup> Ohno<sup>7</sup> and Garry.<sup>8</sup> Those who have found that morphine stimulates the small intestine are Nasse,<sup>9</sup> Pal,<sup>10</sup> Popper,<sup>11</sup> Trendelenburg,<sup>12</sup> Behan,<sup>13</sup> Macht,<sup>14</sup> Uhlmann

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and Abelin,<sup>15</sup> Baur,<sup>16</sup> Tscherkess,<sup>17</sup> Gordonoff,<sup>18</sup> Plant and Miller,<sup>19</sup> Gruber and Robinson,<sup>20</sup> Dreyer,<sup>21</sup> Dvorak and his associates<sup>22</sup> and Wilen and Dragstedt.<sup>23</sup>

A few of the aforementioned authors merit special consideration, since they have secured results with the intestine under as nearly normal conditions as possible. Pal,<sup>10</sup> in 1900, appears to have been the first to record the contractions of the intestine *in situ* by means of a balloon in the intestine. He observed the effect of morphine on curarized dogs in doses of from 0.02 to 0.1 Gm. for a dog weighing from 6 to 8 Kg. The tone and the peristaltic movements of the small intestine were increased. Plant and Miller<sup>19</sup> prepared dogs with Thiry-Vella loops and made kymographic records of the small bowel. They found an increase in tone, an increase in the amplitude of segmentation movements and an increase in the amplitude and frequency of peristaltic waves. With doses of 0.5 mg. per kilogram, the effect disappeared in from five to eight hours, while with large doses of 5 mg. per kilogram, the duration of effect was twelve hours or more. In a man with a scrotal hernia, the number of contractions of the small intestine was increased by morphine. Gruber and Robinson,<sup>20</sup> also working on dogs with Thiry-Vella loops, noted essentially the same results as Plant and Miller with the use of morphine. Large doses decreased the general tonus and in some cases increased the force of rhythmical contractions. Dreyer,<sup>21</sup> by using the balloon method in cats, found that morphine in

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doses of 4 mg. per kilogram increased the tone and excursion of the recording kymograph lever. Dvorak and his associates <sup>22</sup> studied the effect of morphine on the human intestine by inserting a balloon into patients who had an ileostomy. After giving 10 mg. of morphine intravenously, an increase in tone and peristaltic waves was recorded. Similar results were obtained with ileostomies and colostomies on dogs with a dosage of 20 mg. of morphine given intravenously. The increase in activity could be easily determined by auscultation. Dogs in which obstructions were produced showed essentially the same results after the administration of morphine as those with normal bowels. With 50 mg. of morphine the intestinal noises were not so loud as with smaller doses. Wilen and Dragstedt <sup>23</sup> produced experimental peritonitis in dogs and recorded the results with a balloon placed in the bowel or in Thiry-Vella loops. Observations were also made on patients with peritonitis by auscultation of the abdomen. Both experimental and clinical observations showed that morphine increased the intestinal activity.

That morphine causes a spasm of the sphincters is agreed by all who have studied the subject. A great many experiments have been made on animals and a considerable number on human beings, and the emptying time has been prolonged several hours in the average case. Hirsch,<sup>24</sup> Baas,<sup>25</sup> Krylow,<sup>26</sup> Magnus,<sup>27</sup> Van den Velden,<sup>28</sup> Padtberg,<sup>29</sup> Arnsperger,<sup>30</sup> Schwenkenbecher and his co-workers,<sup>31</sup> Schwenter,<sup>32</sup>

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Mahlo,<sup>33</sup> Stierlin and Schapiro,<sup>34</sup> Katsch,<sup>35</sup> Macht,<sup>36</sup> Gordonoff<sup>18</sup> and Thomas<sup>37</sup> have found an increased emptying time of the stomach after the administration of morphine. Of the foregoing investigators, Magnus, Arnsperger and Stierlin and Schapiro have found an increase in the emptying time of the ileum.

The foregoing reports indicate that a general review and revision of our ideas concerning the effect of morphine on the gastro-intestinal tract are advisable. Experiments were planned partially to review the work of Plant and Miller, to determine the effect of morphine on the obstructed small intestine under the most favorable conditions and to study the action of morphine on the pyloric and ileocecal sphincters.

# EXPERIMENTS

*Effect of Morphine on the Small Intestine.*—For the purpose of studying intestinal activity after the administration of morphine sulphate, five dogs were prepared with Thiry-Vella loops of the upper jejunum and five dogs with Ivy-Mann enterostomies as previously described.<sup>36</sup> When healing had occurred, tracings of the intestine before and after the administration of morphine sulphate were obtained by the use of the Brodie bellows with an air pressure medium at a constant measured pressure. All morphine was given subcutaneously. Obstructions were then made in the upper jejunum 15 cm. below the ligament of Treitz, and the effect of a daily dose of morphine on the normal intestine of the dogs with Thiry-Vella loops and on the obstructed intestine of the dogs on which Ivy-Mann enterostomies had been performed was studied.

Morphine in small and moderate doses increased the tonus, the amplitude of segmentation movements and the amplitude and frequency of peristaltic waves in the jejunum and ileum of the dogs (fig. 1). The jejunum showed the more marked response. Morphine in doses of

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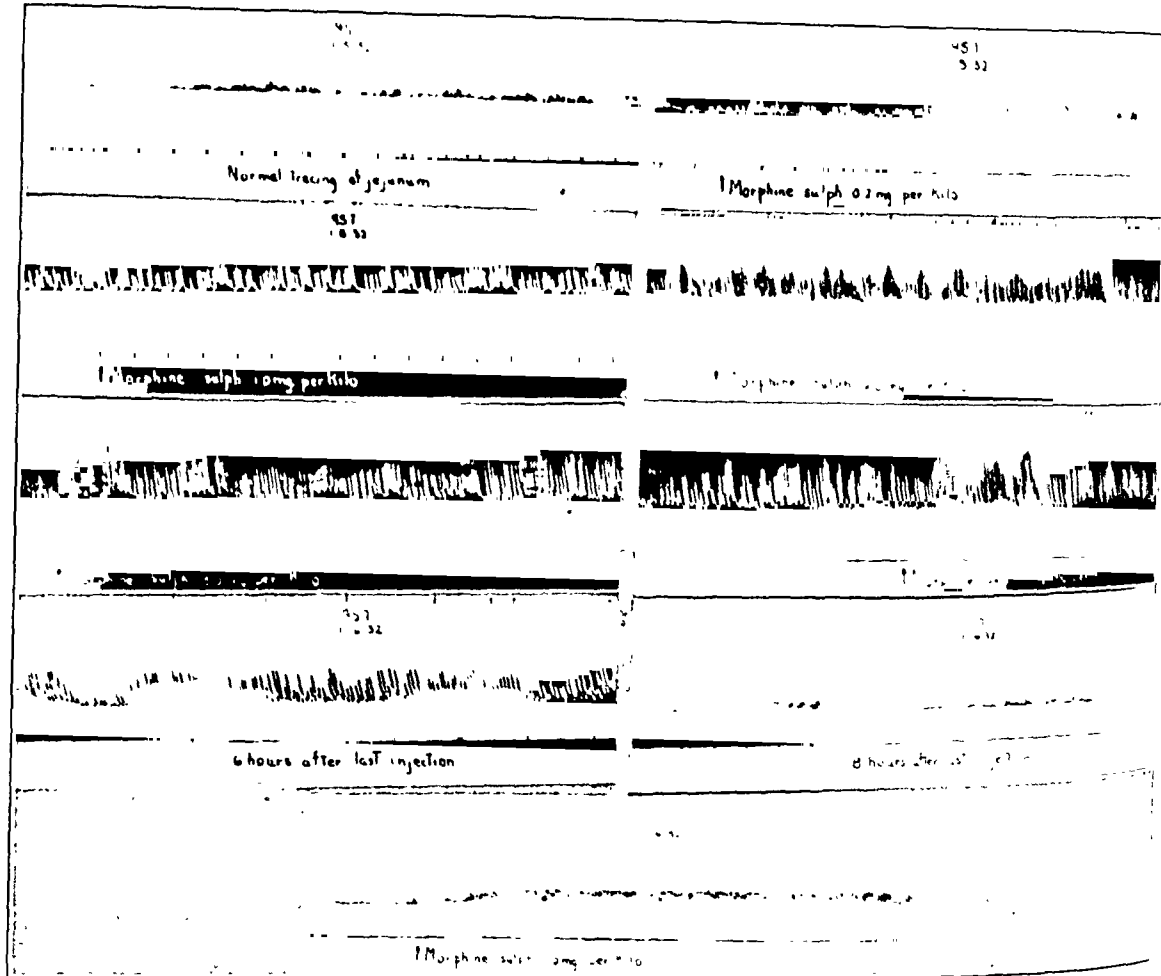


Fig. 1.—Kymographic tracing of jejunum from Thiry-Vella loop, showing effect of increasing doses of morphine when given hypodermically. The intestine showed some activity eighteen hours after the last injection.

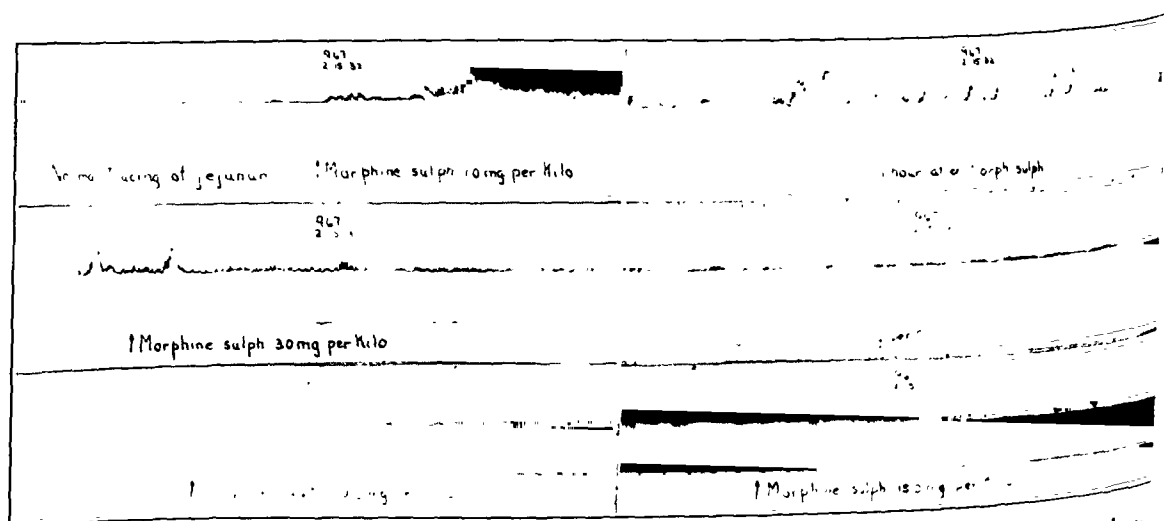


Fig. 2.—Kymographic tracing of jejunum from Thiry-Vella loop after the giving of large doses of morphine hypodermically. The larger doses caused a decrease in peristalsis, but did not diminish the rhythmic contractions.

from 3 to 5 mg. per kilogram stopped peristalsis and somewhat decreased the tone without affecting segmentation movements (fig. 2). Very large doses increased the amplitude of the segmentation movements, but peristalsis did not return. The duration of the effect of morphine was about six hours for the small doses (0.5 mg. per kilogram) and twelve hours for the larger doses (5 mg. per kilogram). The administration of morphine to dogs with Thiry-Vella loops or with

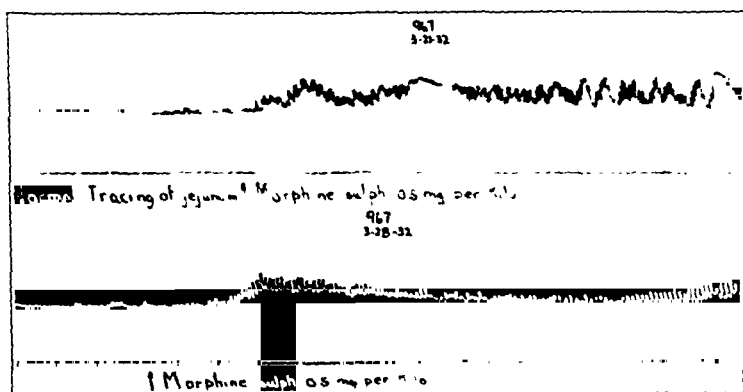


Fig. 3.—Obstruction of jejunum. Tracing made from Thiry-Vella loop independent of obstruction. Records made after the administration of morphine hypodermically one and seven days after obstruction.

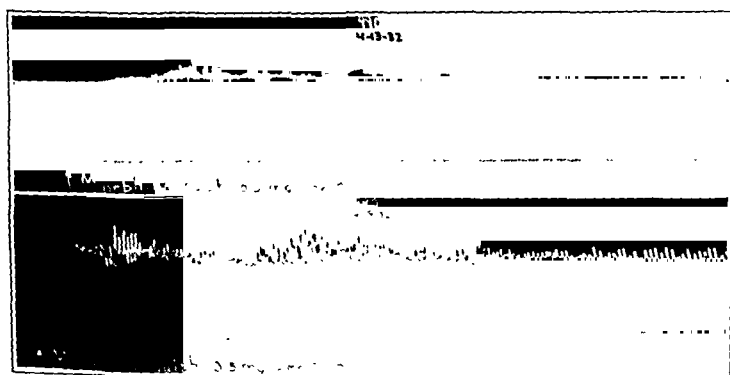


Fig. 4.—Obstruction of jejunum. Tracing of jejunum made just above the obstruction through an Ivy-Mann enterostomy. Records made one and six days after obstruction.

Ivy-Mann enterostomies in which the upper jejunum had been obstructed produced the same effect on the intestinal movements as that shown in normal animals (figs. 3 and 4). There did not seem to be any decrease or increase in the response as death approached.

As controls and for comparison, tracings of the jejunum were made after the administration of codeine sulphate, strychnine sulphate and

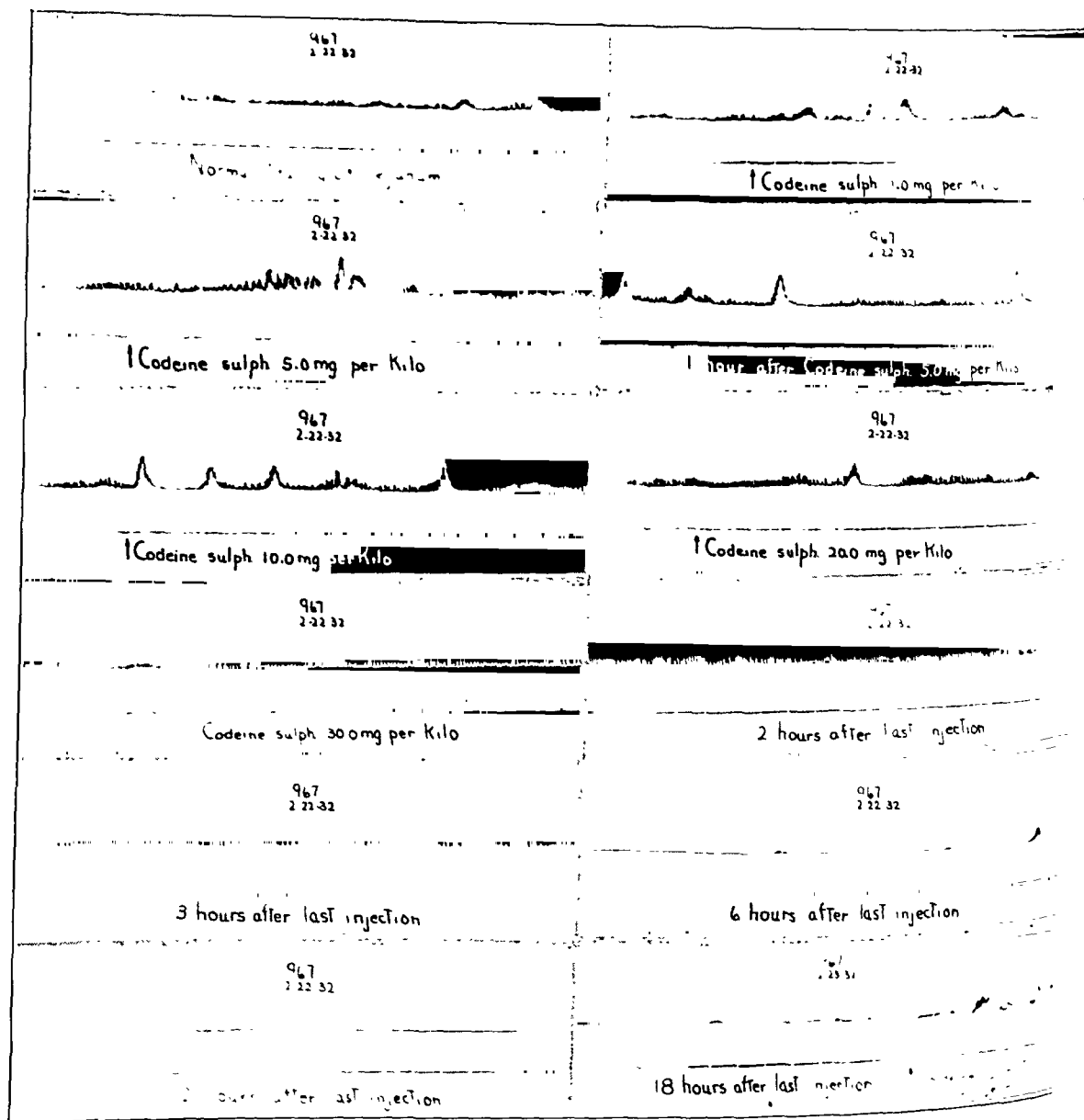


Fig. 5.—Kymographic tracings of jejunum from Thiry-Vella loop. Codeine sulphate was given hypodermically in gradually increasing doses. Note the decrease in peristalsis after large doses. The rhythmic contractions continue as long as the effect of codeine lasts. Eighteen hours after the last large dose of codeine the intestine was again stimulated by a small dose.

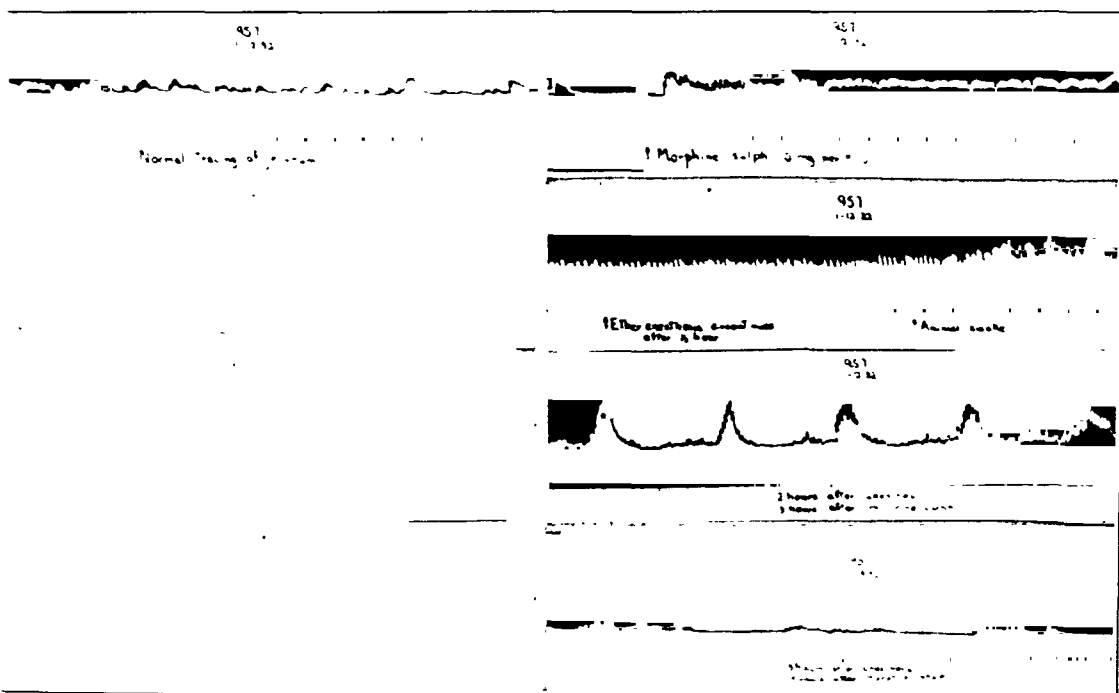


Fig. 6.—Tracing of jejunum from Thiry-Vella loop, showing effect of ether anesthesia after the intestine has been stimulated with morphine. The effect of the morphine persists longer than the effect of ether.

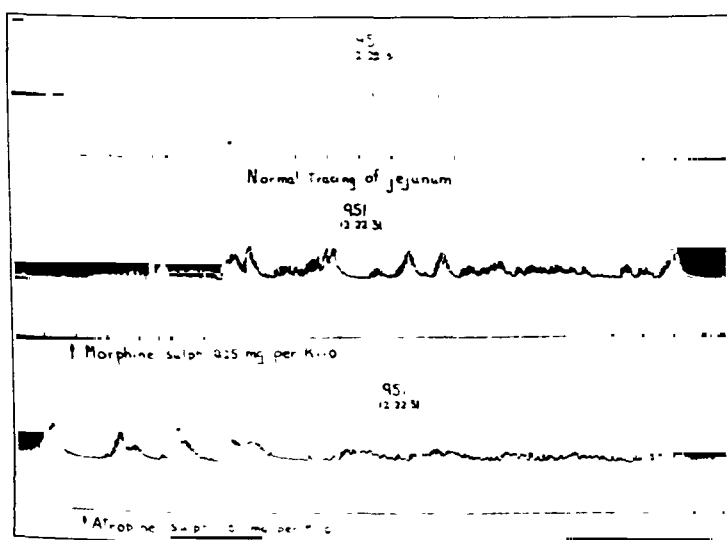


Fig. 7.—Kymographic tracing of jejunum from Thiry-Vella loop, showing the depressing effect of atropine after the intestine is stimulated with morphine.

atropine sulphate by hypodermic injection and of ether by inhalation (figs. 5, 6, 7 and 8).

In a patient on whom ileostomy had been performed, morphine in doses of from  $\frac{1}{6}$  to  $\frac{1}{2}$  grain (0.01 to 0.03 Gm.) increased the size and frequency of the intestinal movements. Auscultation showed great activity of the intestine, and the increased effect after morphine could also be observed directly on the protruding intestine at the site of the enterostomy. Certainly auscultation and the appearance of the intestine were just as striking as in the dog. Auscultation of four normal abdomens, of one case of intestinal obstruction, of four cases of severe generalized peritonitis and of two cases of uncomplicated paralytic ileus showed a marked increase in intestinal noises after the

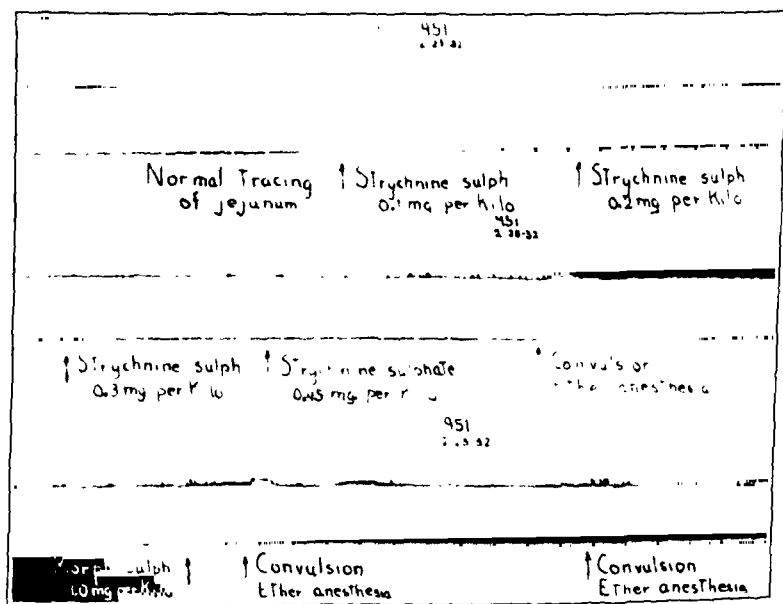


Fig. 8.—Kymographic tracing of jejunum from Thiry-Vella loop, showing the absence of effect of strychnine sulphate given by hypodermic injection. There was no appreciable response after a dose sufficient to produce convulsions.

usual administration of  $\frac{1}{4}$  grain (0.016 Gm.) of morphine. Further studies of intestinal peristalsis in patients were made by observations of three with large hernias. Increased peristalsis was striking in all of these patients following the hypodermic injection of  $\frac{1}{4}$  grain of morphine.

*Effect of Morphine on the Sphincters.*—A dog that was free from intestinal parasites was given a barium meal of 100 cc., and the normal emptying time of the stomach was determined. The following three days the dog was given a subcutaneous injection of morphine, 0.5 mg. per kilogram of body weight, and fifteen minutes after each dose a barium meal was given. The normal emptying time of the stomach

was found to be two hours. After the administration of morphine, a marked retention was present after two hours. Emptying occurred in four hours.

Twenty cubic centimeters of thick barium was introduced into a dog on which ileostomy had been performed, and the normal emptying time of the ileum was determined. The following day an injection of 0.5 mg. of morphine sulphate was given before the injection of barium. Normal emptying of the ileum was found to be complete in two hours. After the administration of morphine, all of the barium remained in the ileum at the end of two hours.

A patient who had a normal emptying time of the stomach was also given  $\frac{1}{4}$  grain of morphine followed by a barium meal. There was marked retention six hours after the administration of morphine.

#### SUMMARY

1. The effect of morphine sulphate on the movements of the jejunum in dogs was studied by means of kymographic tracings taken with a balloon in Thiry-Vella loops, through Ivy-Mann enterostomies of the upper jejunum, and of the ileum through an ileostomy. The effect of morphine on the normal and obstructed small intestine was also studied.

2. The effect of morphine on the movements of the small intestine in human beings was studied by means of tracings taken with a balloon through an ileostomy opening, by observations of large hernias and by auscultation of both the normal and the pathologic abdomen.

3. The effect of morphine on the sphincters of the intestine in dogs and in man was studied by means of the x-rays.

4. Morphine sulphate in ordinary doses gives an increase in tone, an increase in the amplitude of segmentation movements and an increase in the frequency and amplitude of peristaltic waves. Large doses stop peristalsis and decrease the tone, but segmentation movements are little affected and may be somewhat increased. The duration of the effect of an average dose of morphine on the intestine is about six hours. This is true for both animals and man.

5. Morphine stimulates the obstructed intestine as well as the unobstructed intestine in animals as recorded by the kymograph, and in man and animals as determined by auscultation. There appears to be no increase or decrease in response to morphine as death approaches.

6. A single dose of morphine caused retention of the barium meal in the animal and in the human stomach. The emptying time was at least twice the normal. A marked delay in the emptying of the ileum in the dog was noted. Morphine evidently produces a spastic action on the sphincters which delays the progress of barium through the gastrointestinal tract.



# CANCERPHOBIA

## SPECIAL RELATION TO INSIGNIFICANT AND FANCIED LESIONS OF THE TONGUE

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The purpose of this communication is to call attention to the increasing frequency of cancerphobia, especially as seen in patients with minor complaints referable to the tongue.

Cancer propaganda has greatly increased the number of people who present themselves to the physician regarding a benign or early new growth. However desirable this state of affairs may be, it has added considerably to the difficulties and responsibilities of the medical profession. More than ever, clinicians must be alert to make a correct diagnosis in patients who may present little in the way of signs and symptoms. A small neoplasm often intrudes so slightly on the organism that its detection may call for the greatest diagnostic acumen. MacFee<sup>1</sup> has recently pointed out that a number of examiners fail to discover lingual carcinomas before they have progressed to an advanced stage. On the other hand, the patient may not have an organic disease, but to arrive at such a decision may be exceedingly difficult. Thus, one may be puzzled as to the absence or presence of an organic disorder, and, when the latter has been established, its malignancy or benignancy may furnish a perplexing problem.

After the malady has been correctly evaluated, proper treatment assumes paramount importance. Sometimes it is no easy matter to convince the patient that his ailment is unrelated to cancer. When a benign tumor is disclosed, the mere fact that objective treatment is instituted may serve to reassure the patient; but, if no physical abnormality is revealed and nothing is done, the fears of the patient may be increased to such an extent that they may be dispelled only by a high degree of sympathy, understanding, and patience on the part of the physician. In some instances simple reassurance from the medical attendant will permanently and wholly allay the person's anxiety. In many other cases a careful, detailed explanation must be given to the patient in order

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1. MacFee, W. F.: Concealed Cancer of Tongue, *Ann. Surg.* **93**:481, 1931.

to convince him that he is not afflicted with cancer. In a busy clinic it often happens that insufficient time is devoted to this task, and the patient departs with such mental anguish that he forsakes his work and enters on a vicious circle of medical shopping. Thus industrial and economic problems may be introduced as well as a reduplication of effort on the part of various physicians and medical organizations. Therefore, it devolves on those who first examine these sufferers to do all that is possible for their peace of mind and to inaugurate whatever is indicated in the way of treatment, even though the latter may be simple and designed for psychic effect. Experience teaches that the response on the part of the patient amply justifies any special attention that may be given to his problem. Indeed, there are few, if any, fields in medicine where the physician may better practice the art of his profession.

Apparently, neither Ewing<sup>2</sup> nor Roussy<sup>3</sup> has emphasized the recent increase of cancerphobia. Rose<sup>4</sup> and Marshall<sup>5</sup> have briefly noted the occurrence of cancerphobia in relation to hypersensitiveness and hypertrophy of the lingual foliate papillae. Fitzwilliams<sup>6</sup> has mentioned the same condition. In some of the patients on whom the present study is based the complaints were analogous to those described by the three aforementioned authors, but in others the setting was entirely different.

Zagni<sup>7</sup> and a few others have called attention to glossal papillomas, but their patients consulted the physician because of the increase in the size of the lesion and not on account of any morbid fears connected with the ailment. In such an instance, the objective findings were of main interest, whereas in the present group the subjective features were of paramount importance.

In our cases, even the immediate exciting cause for the hypersensitiveness was sometimes obscure. Occasionally, an ill-fitting dental plate or a rough tooth irritated the area. Not infrequently, the foliate papillae were slightly or moderately enlarged (fig. 1). In some instances no abnormality could be detected.

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2. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

3. Roussy, G.: *Le Cancer*, in Roger, C. H., et al.: *Nouveau traité de médecine*, ed. 2, Paris, Masson & Cie, 1929, vol. 2, part 5.

4. Rose, B. T.: *A Note on the Hypertrophy of the Papilla Foliata in Man*, *Lancet* 2:14, 1927.

5. Marshall, C. J.: *The Papillae Foliatae and Carcinophobia*, *Brit. M. J.* 2:13, 1928.

6. Fitzwilliams, D. C. L.: *The Tongue and Its Diseases*, London, H. Milford, 1927.

7. Zagni, L.: *Papilloma della lingua*, *Riforma med.* 42:871, 1926.

The women outnumbered the men and were usually of a very nervous temperament.

#### STATISTICAL STUDIES

Since no adequate data were available concerning patients who had been turned away with the diagnosis of "no significant lesion" and whose complaint was merely slight pain or sensitiveness, it seemed worth while to scrutinize the records of patients when the clinical diagnosis of a common, benign lesion of the tongue had been confirmed by microscopic studies. It seemed that if such a pathologic process represented the worst type of benign lesion, so far as the later development of cancer might be concerned, disorders of lesser note should entail fewer chances of subsequent malignant changes taking place.

In this connection, Fitzwilliams<sup>6</sup> stated that papilloma is the "commonest simple tumor of the tongue," and when it appears in middle life he regards it with distinct suspicion. Ewing<sup>2</sup> stated that in papillomas of the tongue "there is a strong tendency toward malignant change," and that "a large proportion of lingual carcinomas exhibits a brief preliminary papillomatous stage." Thus it would seem that a review of distinctly suggestive papillomas of the tongue might yield some information concerning the likelihood of a carcinoma becoming engrafted on a benign lingual lesion.

By studying the laboratory records in the department of pathology, the following facts were disclosed. From 1918 to 1923, inclusive, biopsies were performed on nine glossal papillomas, and from 1924 to 1928, inclusive, thirty-one similar diagnoses were recorded. The total number of forty cases for the eleven-year period was surprisingly small, but the distinct upward increase for the past few years was well indicated. In only twenty-three of the aforementioned records were there sufficient data to warrant their being used, and in eight of these cases the condition was sooner or later histologically diagnosed as carcinoma.

This left a group of fifteen cases in which (during the period of observation) the lesion remained unquestionably benign. Six of these patients were women. The average age for both sexes was 50 years; the patients were thus within the period when Fitzwilliams<sup>6</sup> would regard all papillomas of the tongue with suspicion. Most of the complaints were pain or "irritation" of the affected region. Only one patient had a positive Wassermann reaction. Bad teeth and poorly fitting dentures were usually found.

From the foregoing small amount of evidence one may surmise that even when the papillomas were so atypical that cancer could not be

ruled out of the clinical diagnosis, carcinoma never developed in 66 per cent of the patients within the observation period. From such facts one may deduce that lesions of much less significance than papillomas, as exemplified by sensitive areas or a simple hypertrophy of the mucous membrane, will be far less likely to give rise to cancer, therefore the patient should be completely reassured with the hope that all of his fears may be adequately dispelled.

Naturally, the aforementioned opinion does not hold for the 35 per cent of the patients who did have a malignant process. They are in an entirely different category, and should have proper, intensive, objective treatment with much less relative emphasis being placed on psychotherapy or symptomatic measures.



Fig. 1.—Posteriorly, along the left border of the tongue, were some enlarged foliate papillae. A similar condition existed on the right side. The remaining upper teeth may be seen. This photograph was taken during the patient's first visit to the hospital.

#### CLINICAL STUDIES

Perhaps the signs and symptoms presented by many patients who have cancerphobia due to a fancied or benign lesion of the tongue may be demonstrated best by two case histories, each fairly typical of certain members of the group.

#### REPORT OF CASES

CASE 1.—*History.*—M. K., a white woman, aged 50, married, complained of having a lingual "cancer." Four months before coming to the hospital she had noticed a laceration on the left side of the tongue and had attributed it to the impingement of a tooth. During this time she had pain in the lumbar region and consulted a physician, who recommended the extraction of certain teeth. She complied, but obtained no relief from the rachiodynia. Following this a sensation of "roughness" developed in the foliate papillae, and a "sore" spot appeared on the

end of her tongue. One week before presenting herself at the clinic, her physician advised her coming to the hospital, saying that she "might have a bad disease." Her husband then forbade her to prepare his food, and added to her fears by telling her that she had a cancer and would have her tongue taken out. When an acquaintance supported her husband's dire predictions, she hastened to the hospital. The past history and family history seemed irrelevant.

*Physical Examination.*—The patient was well developed, slightly obese and extremely apprehensive. She appeared to be in good physical condition, and presented no defects aside from those to be set forth. The tongue was of normal size, shape, color and consistency. Its tip was hypersensitive. The foliate papillae on each side were moderately hypertrophied and slightly tender (fig. 1). The buccal mucous membrane appeared normal. She had a few lower and upper teeth, all of which were carious and loose. Gingivitis was marked.

*Treatment.*—The patient was advised to eat nothing but bland foods, to have several of the remaining teeth extracted, and to return within two weeks, or sooner



Fig. 2.—This picture depicts the same patient as in figure 1, and was taken eighteen months later. By comparison it will be seen that four of the upper teeth have been removed, and that the foliate papillae have become slightly flattened.

if she wished. She was told positively that she did not have cancer and need not have the slightest worry about that. She departed in a happy frame of mind.

*Course.*—The patient was followed up at fortnightly intervals. Her anxiety reappeared several times, but it became increasingly easier to dispel, and finally she became thoroughly convinced that she was not suffering from cancer. When she was last seen (one and one-half years later), she had only slightly less enlargement and tenderness of the foliate papillae (fig. 2) and fewer teeth than when she first came under observation; her complaint was one of financial difficulties without reference to any physical ailment.

This case illustrates the type of lesion that is perhaps most often associated with cancerphobia of the tongue. Hypersensitivity and enlargement of the foliate papillae are not dangerous in themselves, but their annoyance to the patient and the usual inattention given to the psychic side of the case by the physician lends to them an exaggerated importance. In some instances it may be necessary for the mental, as

well as the physical, relief of the patient to remove or destroy the offending area.

*CASE 2.—History.*—M. W., a white woman, aged 68, married, complained of xerostomia and tenderness of the tongue which had been present for the past seven months. She was afraid that she had a lingual "cancer." Her malady had been progressive. Various mouth washes prescribed by physicians had seemed to increase the abnormal sensitivity, and recently the throat had become involved. Of late, the glossal tenderness had increased so that she could scarcely eat, and her sleep was disturbed by sharp, sticking sensations throughout the tongue, the tip of which rested against an upper dental plate. She was convinced that she had cancer and that little, if anything, could be done to alleviate her condition. Her habits, including those of drinking and eating, had been normal. During the past eight years she had unaccountably lost 15 pounds (6.8 Kg.) in weight. Thirty-four years previously she had "neuritis" in both upper members, which disappeared after "injections in the arms." She had had an upper dental plate for the past twenty years and a lower denture for five years. At 65 years of age, her father died of "dropsy and rheumatism," and her mother succumbed to tuberculosis in her twenty-fifth year. The marital history was irrelevant.

*Physical Examination.*—The patient was well developed and moderately well nourished. Her extreme anxiety was apparent. She had 6 lower teeth, 2 of which had gold crowns. The left lower canine was eroded at the gum margin. The dental plates appeared to fit satisfactorily. The openings of the submaxillary salivary gland ducts were elevated and dilated. The entire buccal and pharyngeal mucous membrane was moderately hypersensitive and slightly redder than normal. The tongue was of normal size, shape and consistency; its tip was erythematous, except for a tender yellow area, 2 mm. in diameter and 1 mm. in height. There was moderate hypertrophy of the circumvallate and fungiform papillae, and the lymphoid tissue at the base of the tongue seemed more abundant than normal.

*Laboratory Observations.*—The Wassermann reaction of the blood was negative. The gastric contents during fasting contained no free hydrochloric acid but had a total acid of 8 per cent; thirty minutes after eating two slices of white bread the free hydrochloric acid was zero, and the total acid was 10 per cent. Urinalysis gave negative results, except for many white blood cells and a hyaline cast in the centrifugated sediment. Chemical analysis of the blood showed: blood sugar, 133 mg., and blood urea, 7.4 mg. per hundred cubic centimeters of blood. Smears from the tongue, mouth and pharynx were stained with carbol fuchsin and revealed many variously arranged cocci in large epithelial cells, a few bacilli and a moderate number of white blood cells. Examination of the blood disclosed: hemoglobin, 80 per cent; red blood cells, 3,720,000, and white blood cells, 4,000; a differential count showed 50 per cent polymorphonuclear neutrophilic leukocytes, 18 per cent large lymphocytes and 32 per cent small lymphocytes. The shape and size of the red blood cells were normal. No explanation was discovered for the slight anemia.

*Treatment and Course.*—The patient was told that she certainly did not have cancer, and her immediate relief was gratifying. No medications were allowed. She was directed to eat bland foods and was given a list from which to select them. She was instructed to keep an accurate dietary record and to bring it to the hospital at each weekly visit.

For a few months the patient improved rapidly, and most of the symptoms disappeared. She was last heard from two and a half years after her first visit to the clinic. She still had complaints concerning her tongue, mouth and throat, and considered that she was in poor health, but she did not have any fear concerning cancer.

This case exemplifies a condition in which the objective findings are slight, but the subjective features are pronounced. Despite the failure to relieve the patient of her symptoms more than temporarily, she had no recurrences of the cancerphobia, which was the primary cause of her presenting herself at the clinic. The case is reported from that standpoint, and not from that of giving the patient relief from the



Fig. 3.—The tongue was removed in toto at autopsy and fixed in a 10 per cent solution of formaldehyde. The photograph illustrates where the sections were taken for histologic study.

underlying disease.<sup>8</sup> One should essay the latter, and careful inquiry should be made into the cause of the xerostomia and stomatodynia in order to remove or lessen the fundamental pathologic condition. The emotional side must be closely studied, for it is often the key to the situation. However, physical defects should be carefully searched for, as they may constitute the exciting, if not the underlying, derangement, and their elimination may effect a cure or betterment.

8. An extended absence followed by the acceptance of a post in another city nullified the author's intention to attempt this accomplishment.

## HISTOLOGIC STUDIES

It is common knowledge that, in addition to its special functions of speech and taste, the tongue is one of the most sensitive parts of the body. In patients suffering from cancerphobia in relation to the tongue, hyperesthesia is a prominent feature, and in some cases this is associated with annoying disturbances in taste. Biopsy usually shows surprisingly little to account for the symptoms. On the other hand, one may see gross lesions of various degrees and types which give little or no concern to the patient because no unpleasant sensations are connected with them.

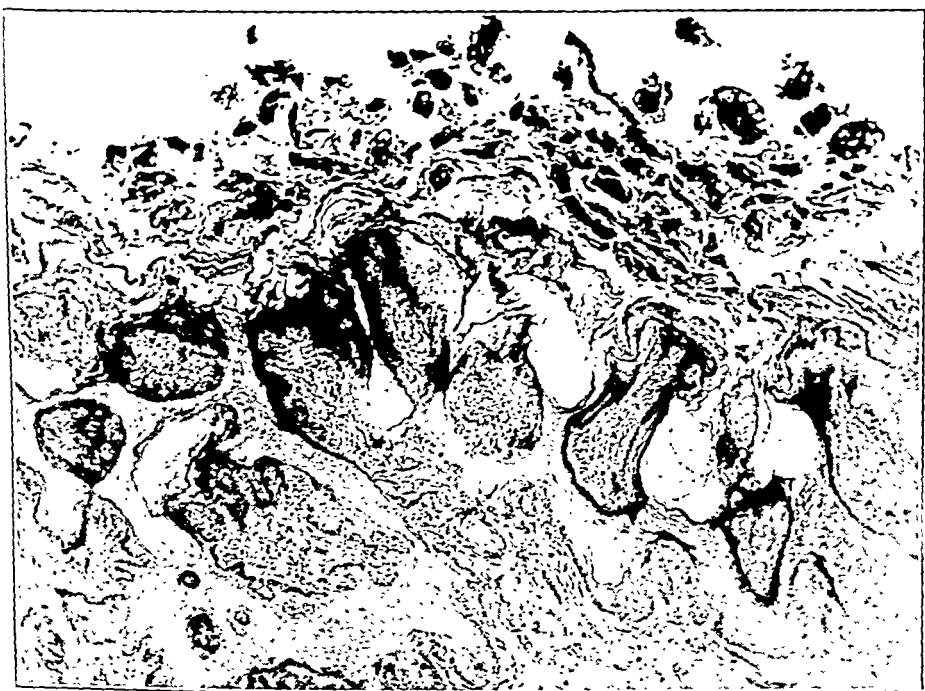


Fig. 4.—Beyond the hornified epithelium covering the tongue there was a considerable collection of inspissated mucus, masses of bacteria and partially disintegrated cellular material ( $\times 55$ ). There were no lingual symptoms.

In a study of autopsy material, sections were taken from four regions of one hundred tongues (fig. 3). Not infrequently microscopic lesions could be demonstrated which were far greater than those in patients afflicted with cancerphobia resulting from paresthesias, tiny ulcers, slight hypertrophy of the mucous membrane or mild gustatory derangements. In none of the patients on whom necropsy was performed had there been any complaints referable to the tongue, and they had died from diseases which had no connection with the mouth, throat or nose. It was hoped that such a study might give some clue to the



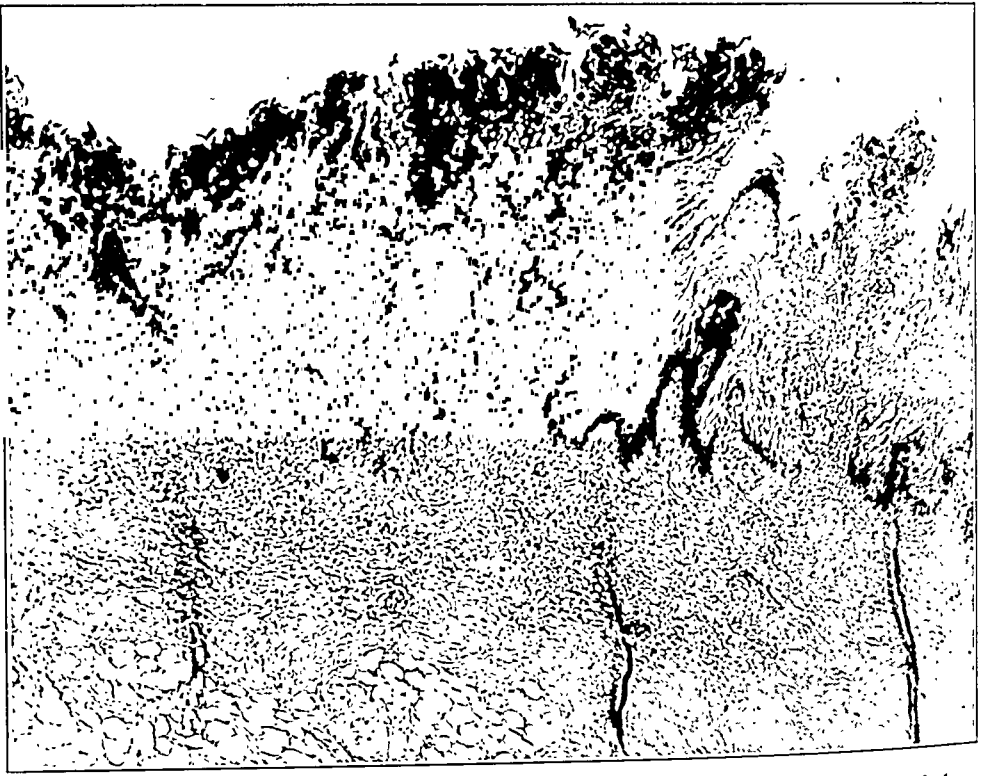


Fig. 5.—This photomicrograph reveals marked necrosis and suppuration of the lingual mucosa and adjacent, underlying tissue ( $\times 72$ ). The patient had no symptoms referable to the tongue.



Fig. 6.—In the lower central portion of the photomicrograph ( $\times 72$ ), there may be seen a distinct loss of the epithelium without any associated infection. The patient had no complaints concerning his tongue.

amount of damage which the tongue may sustain without the person being aware of it.

The amount of microscopic débris that collected on the surface of a normal-appearing tongue was astonishingly great. When sordes was clinically present, this accumulation became enormous. In both instances there was a mixture of cast-off epithelium, food, bacteria and mucus (fig. 4).



Fig. 7.—This photomicrograph ( $\times 30$ ) depicts a glossal papilla in the process of extrusion. Sufficient hypertrophy of such a structure could lead to the formation of a true papilloma. The tongue from which this section was taken was normal.

Erosions of the mucous membrane were not uncommon, and occasionally the associated infection was considerable (fig. 5), while in some it was entirely absent (fig. 6). In other areas the epithelium was hyperkeratotic but well preserved. Many papillae were hypertrophied, and varying degrees of extrusion were seen (fig. 7).

Numerous nerves were observed in the submucosal tissue, but no lesions were revealed with the use of hematoxylin and eosin stain. The mucous glands, with their ducts, were normal and abundant. The muscle and connective tissue revealed no pathologic process. In the posterior portion of the tongue the lymphoid tissue was bulky and covered by thin squamous epithelium.

#### COMMENT

Determination of the cause and treatment of cancerphobia are not usually simple matters. The malady is sometimes the result of an easily recognized organic lesion which can be eradicated. In other instances the underlying physical factor may be so obscure as to tax the powers of the most ingenious diagnostician and to place him in a very difficult situation, for he must properly evaluate the condition before intelligent treatment may be instituted. Therefore, the greatest problem is encountered in patients who have an insignificant or a fancied lesion. An underlying cause must be ferreted out and therapy directed toward that cause. One cannot overemphasize the need for taking the complaints of the patient seriously, and effectively aiding him, lest he become a victim of morbid fear and a burden to those about him.

It is a fact that the malignancy or benignancy of practically all demonstrable lesions of the tongue can be correctly diagnosed by a capable, experienced physician, especially if he resorts to laboratory aids and clinical consultations. Hence, when one is sure that the lesion is not cancer, it is wise to assert such a conviction in order that the patient may receive the benefit of a wholehearted assurance.

The tongue is supposedly a common site for papillomas. In fact, the normal papillae are miniature forms of such a structure, and therefore their enlargement readily results in a true papillary tumor. And yet, from the statistical data at our disposal, it has been indicated that true lingual papillomas are rarely encountered in the pathologic material of the hospital. From this it may be assumed that most people who have had ordinary papillomas of the tongue have not found their way into a hospital for patients with cancer but have been cared for by other medical agencies. It is difficult to ascertain in how many of these a malignant process developed. However (in this series), of the patients who have had papillomas of the tongue so distinctly suggestive that carcinoma could not be ruled out of the clinical diagnosis, 65 per cent did not have cancer within the period of observation. The other 35 per cent probably included a goodly number of patients with papillary carcinomas, but the original biopsy was too superficial to give the true picture. It would seem, then, that the ordinary benign glossal papilloma could be easily and safely removed, and that the clinical findings supported

by a histologic diagnosis would justify the physician in making positive statements in order to allay any associated cancerphobia. Again, it might be emphasized that one should know his ground, but, knowing it, should not be afraid to tread on it.

Cancerphobia attendant on a simple hypertrophy of the foliate papillae which does not reach the stage of a true papilloma may ordinarily be effectively dealt with by some method other than extirpation or destruction *in situ*, but the latter procedures may be performed with good results, thereby removing an objective feature.

Hypersensitivity and pain may be associated with xerostomia and no cause found for either. Usually such a condition is hard to cope with and will call for patient, long-continued, intelligent treatment. If no physical basis can be found, a close study of psychic factors may reveal the key to the situation.

In the light of newer knowledge concerning the participation of the sympathetic nervous system in the phenomena of pain, it should be exceedingly interesting to induce a temporary block with procaine hydrochloride and to witness the effect, if any, that would be produced on the patient's symptoms. If success were obtained, it would then be feasible to inject alcohol into the sympathetic ganglions or to extirpate them. Moreover, one might try blocking the sensory nerves to the area if the interruption of purely sympathetic pathways gave no relief.

The fact that people have gross and microscopic lesions of the tongue without disturbances in sensation is further evidence that nervous or psychic disorders rather than organic ones constitute the essential derangement in cancerphobia.

The tongue is subject to continuous trauma and infection. The amount of cellular and other débris is enormous, and at times even whole papillae are cast off. The nerve supply is unusually abundant. The prominence of the organ and consequent easy manner of viewing it, the use of it as an index of general health, its special functions connected with speech and taste, and its high degree of sensitivity all tend to focus the patient's attention on his tongue. These facts, added to the layman's knowledge of the terrible mutilation and high mortality attendant on a glossectomy coupled with his great fear of cancer in any form or region, are sufficient to strike terror into the stoutest heart. It is small wonder, then, that a person of nervous or emotional instability cowers before the possibility of such a scourge and becomes an easy victim of cancerphobia. Such unfortunates present excellent opportunities for the practice of medical art and humanitarianism.

#### SUMMARY

Attention has been called to the increasing number of patients with benign new growths who present themselves. Emphasis has been placed

on those who have developed cancerphobia as a result of an insignificant or fancied lesion of the tongue. Stress has been placed on the responsibility of the physician to make a correct diagnosis as to the existence or nonexistence of a malignant tumor and, in the latter instance, to give special time and thought to dispelling the fears of those who may be suffering from cancerphobia.

Since insufficient, or no, data were recorded in cases in which there was a tiny lesion of the tongue or none, there has been included a short statistical study of lingual papillomas, since they are the commonest in the group of benign tumors of the tongue and are, at the same time, most liable to undergo malignant changes. In the present series, 65 per cent of distinctly suggestive glossal papillomas remained benign throughout their observed course.

As a matter of illustrating signs and symptoms together with a simple form of treatment, the histories of two cases were included. One patient complained of undue sensitivity in the lingual papillae on both sides of the tongue, and the subjective features were eliminated by simple psychotherapy combined with oral hygiene. The other cancerphobist had xerostomia associated with paresthesias of the buccal and pharyngeal mucous membranes, the symptoms being most pronounced over the anterior portion of the tongue. It was possible to reduce temporarily the abnormal sensations and to dispel permanently the patient's fears of having cancer.

In order to obtain histologic data concerning the existence of lesions without associated sensory disturbances, a series of one hundred tongues secured at autopsy was studied. Enlarged papillae, erosions of the mucous membrane, superficial infections and collections of débris were often found. Since no patient had had complaints referable to the tongue, it was assumed that under suitable conditions such lesions as those described may exist without being noticed by the patient.

#### CONCLUSIONS

1. Cancerphobia is apparently on the increase. It should be actively combated by sagacious, patient, sympathetic treatment.

2. Many patients suffering from a morbid fear of lingual cancer have no demonstrable lesion; others have a benign one which is often a simple hypertrophy of the foliate papillae.

3. An analysis of twenty-three cases of lingual papillomas in which malignancy was suspected or could not be ruled out clinically revealed that during the period of observation 65 per cent of the patients did not show carcinomatous changes. From this it is reasoned that patients suffering from far more insignificant, or from fancied, lesions of the tongue have little to fear in the way of these becoming cancerous.

4. A microscopic study of one hundred tongues taken at autopsy demonstrates that patients may have small lesions of this organ without sensory disturbances. This supports the idea that cancerphobia is the resultant of underlying psychic and nervous disorders rather than a fundamental physical derangement.

Since writing this paper, I have found an article entitled "L'organe folié de la langue, cause possible d'un diagnostic erroné de cancer," by A. Lacassagne (*Radio-phys. et radiothérapie* 2:131, 1930) which apparently has a direct bearing on the subject of "Cancerphobia."

# PROGNOSIS IN CARCINOMA OF THE STOMACH

REMOTE RESULTS OF SURGICAL TREATMENT TO JANUARY, 1930

ASTLEY P. C. ASHHURST, M.D.†

AND

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PHILADELPHIA

The literature on carcinoma of the stomach is so voluminous that writers should refrain from adding to the confusion unless they follow some uniform plan of record, such as that proposed by Greenough and Simmons.<sup>1</sup> In analyzing our cases we lay no claim to special success in securing what are apparently a few cures, but present even such modest results as a challenge to a disease which unmolested always carries the patient to his grave with absolute certainty. If it could be shown, for instance, that a patient with cancer of the stomach may live untreated for five years, then our conclusions regarding the efficacy of surgical eradication would be unsound. But lacking such proof, we must rely on the surgical method as the only successful means of treatment.<sup>2</sup>

The stomach is the most common site of human cancer (fig. 1<sup>3</sup>). The statistics from which the diagram in figure 2 was drawn show

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† Dr. Ashhurst died Sept. 19, 1932.

1. Greenough, R. B., and Simmons, C. C.: *Boston M. & S. J.* **185**:253, 1921.

2. We are aware that isolated instances of patients surviving over five years with untreated carcinoma are on record, but not, as far as we know, of gastric carcinoma. Dr. Peter P. Klopp recalls a woman with unmistakable clinical cancer of the left breast in the days before the therapeutic use of radiant energy, who refused treatment, but who nevertheless lived for eighteen years after the diagnosis was made. The longest period of survival in surgically untreated cancer of the stomach that we were able to find in the literature is three years. ((a) Bloodgood, J. C.: *Ultimate Results and Actual Functional Results After the Different Types of Operations After Intervals of Five Years or More*, *Ann. Surg.* **92**:574 [Oct.] 1930; (b) Hitzengerber, K., and Merkler, D.: *Cancer of the Stomach: Fate of Patients Treated at First Medical Clinic, University of Vienna*, *Wien. klin. Wchnschr.* **44**: 632 [May 15] 1931.)

3. The figures from which this drawing was made represent the death rate per hundred thousand, and not the incidence of cancer. According to the medical department of the Metropolitan Life Insurance Company, there are no reliable statistics for the incidence of cancer of the stomach, the best available figures on deaths probably being those furnished by the Annual Reports of Mortality Statistics published by the United States Bureau of the Census (personal communication). However, since the death rate and incidence are so nearly alike, the figure given portrays incidence accurately enough.

that there is an unmistakably significant trend toward an increase in the incidence of this disease, especially among males, who are apparently afflicted more frequently than females, the difference between the sexes widening with the passage of years. Caucasians suffer more often than blacks (fig. 3), and economic station has some bearing, for the more prosperous group seem to suffer less frequently (fig. 2). The age incidence of carcinoma of the stomach in a vast series of cases is shown in figure 3. Our own figures, which follow, show that most of fifty-four patients were in the sixth (eighteen) and seventh (eighteen)

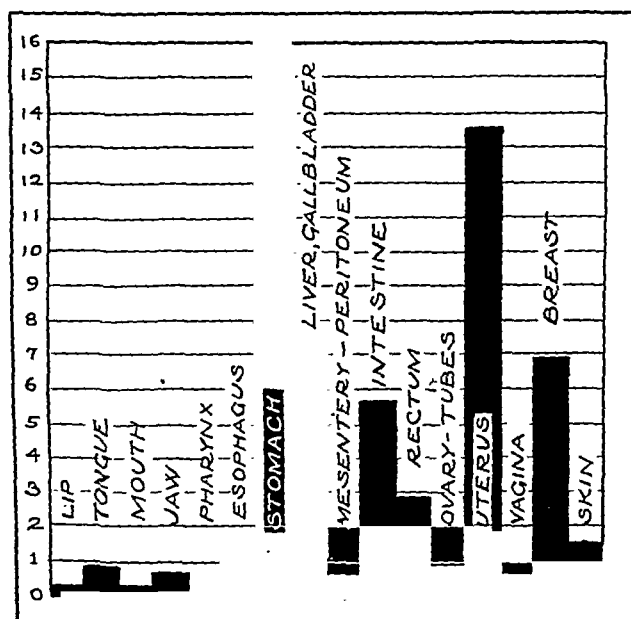


Fig. 1.—Diagram drawn from statistics of the Metropolitan Life Insurance Company, Industrial Department, 1922, showing that the stomach is the most common site of cancer.<sup>3</sup>

decades of life at the time of treatment: third decade of life, two patients; fourth decade, four; fifth decade, eight; sixth decade, eighteen; seventh decade, eighteen; and eighth decade, four.

The significant feature about both sets of figures is the surprisingly high incidence in the young adult, a fact which belies the usual statement in textbooks. Our youngest patient was 27 years of age, the next youngest being 30 and 33 years, respectively. While the average age of patients in our own series at the time of treatment was about 56 years, more than 25 per cent of them were 50 years of age or less. Among the reports of cancer of the stomach in young patients are



those of Mintz's<sup>4</sup> 11 year old boy; Marble's<sup>5</sup> 17 year old girl; Morian;<sup>6</sup> Jones and Scott<sup>7</sup> (five year cure in a 24 year old man), and Nicholson.<sup>8</sup> Osler and McCrae<sup>9</sup> collected six reported cases in persons under the age of 10.

We observed more than twice as many men as women (thirty-eight male; sixteen female).

#### DIAGNOSIS OF CANCER OF THE STOMACH

*Symptoms.*—Patients with gastric carcinoma fall into three groups according to the type of clinical symptoms from which they suffer: (1) those with a short history (i. e., up to six months); (2) those with

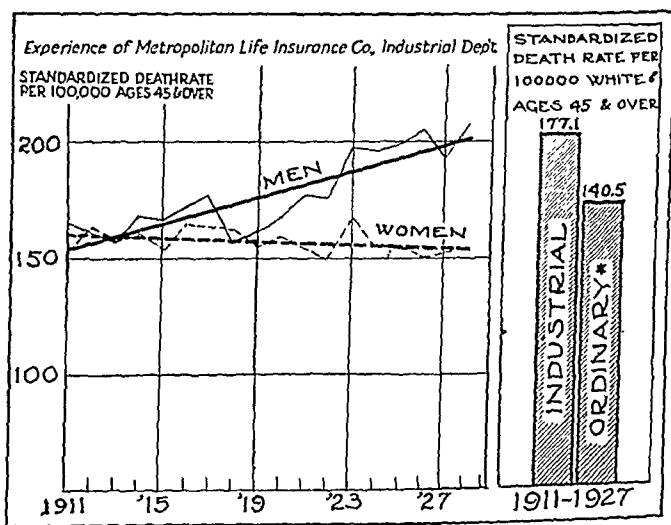


Fig. 2.—Diagram showing how cancer of the "stomach-liver" varies with time, sex and economic station. The star indicates the more prosperous group.

a long history (over six months), and (3) those with no history of the dyspepsia syndrome.<sup>10</sup>

4. Mintz, M. M.: Cancer of the Stomach in 11 Year Old Boy, *Vestnik roentgen. i radiol.* **8**:357, 1930.

5. Marble, A.: Cancer of Stomach in 17 Year Old Girl, *Bull. Johns Hopkins Hosp.* **48**:39 (Jan.) 1931.

6. Morian, R.: Cancer of the Stomach in Young Persons, *Arch. f. klin. Chir.* **164**:329, 1931.

7. Jones, E. B., and Scott, M.: Cancer of the Stomach: Case with Apparent Cure, *M. J. Australia* **1**:554 (April 26) 1930.

8. Nicholson, S. T.: Consideration of Certain Diagnostic Features of Cancer of the Stomach, *Pennsylvania M. J.* **34**:169 (Dec.) 1930.

9. Osler, W., and McCrae, T.: Cancer of the Stomach in the Young, *New York M. J.* **71**:581 (April 21) 1900.

10. Berger, W.: Cancer of the Stomach: Present Status of Early Diagnosis, *Wien. klin. Wchnschr.* **44**:33 (Jan. 9); 71 (Jan. 16); 108 (Jan. 23) 1931.

Group 1 comprises about from 50 to 60 per cent of all cases in our experience, a figure which agrees with those cited by Dwyer, Blackford and Turner,<sup>11</sup> and by Oberniedermayr and Stahnke.<sup>12</sup>

About 35 per cent of all cases fall into group 2.<sup>10</sup>

According to some authorities with significantly large series, group 3 is composed of from 2 per cent<sup>10</sup> to 18 per cent<sup>11</sup> of all cases. Our ward case 3899 is an example of one of these patients who had no complaint concerning his digestion or stomach, showing how difficult it is occasionally to make a correct diagnosis.

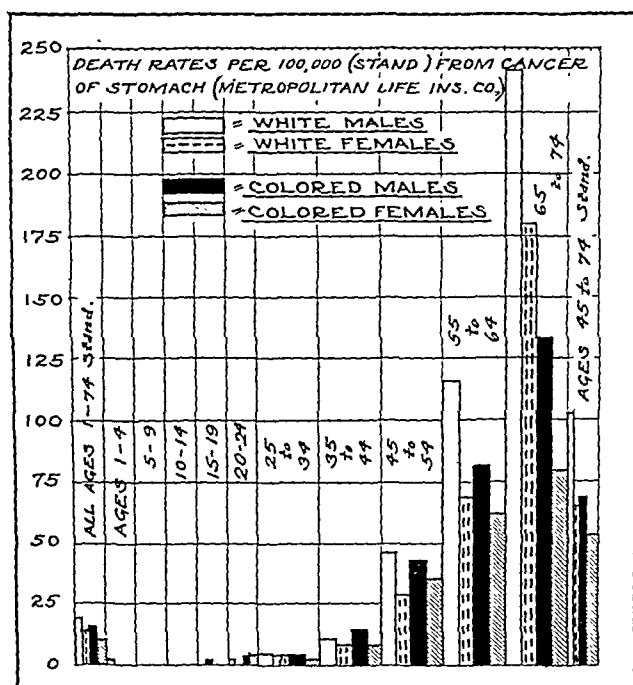


Fig. 3.—Diagram showing how cancer varies with color, sex and age periods.

WARD CASE 3899.—A woman 33 years of age on Feb. 17, 1925, complained of pain in the lumbar region and the pelvis. The presence of carcinoma of the stomach was not even suspected. The patient was examined several times by Dr. Haines (cystoscopy) for ulcerative cystitis, and died a month after admission, of exhaustion and bedsores. Only at necropsy was carcinoma of the stomach (nonobstructive) found, with secondary carcinoma of the pancreas, the lungs and the ovary.

11. Dwyer, M. F.; Blackford, J. M., and Turner, H. C.: Carcinoma of the Stomach: Clinical Study of 100 Cases, *J. A. M. A.* **93**:1456 (Nov. 9) 1929.

12. Oberniedermayr, A., and Stahnke, E.: Carcinoma of the Stomach: Surgical Treatment, 1922-1926, *Koenig's Clinic, Deutsche Ztschr. f. Chir.* **214**:387. 1929.

At first, most of the patients complain of indigestion and lack of appetite, especially for flesh, and loss of strength and weight, rather than actual pain. Later, most of them experience pain, usually in the epigastrium, but not necessarily so, and this occasionally radiates to the lumbar or shoulder region or into the pelvis. The coexistence of epigastric tenderness is common. The prominence of vomiting depends on whether or not there is pyloric obstruction. Those patients in group 3 (without the dyspepsia syndrome) often suffer from weakness and anemia, cardiac disturbances, fever and sweating, or from neuralgia (bone metastasis). The peculiar lemon tint of the skin of anemic patients is said to be characteristic of gastric cancer. The difficulty of diagnosis based solely upon symptomatology is illustrated by the following four cases.

A woman, 48 years of age, who had been under the care of an able neurologist for six months, with the diagnosis of neurasthenia, was found (by exploratory laparotomy, 1925), when a surgeon's advice was finally sought because of failing strength, anorexia and abdominal discomfort, to have an operable mass of carcinoma at the pylorus. Gastrojejunostomy brought symptomatic relief, maintained until the patient's death four months later from lobar pneumonia.

A man of 79 years had lost 42 pounds (19.1 Kg.) during the preceding two years; for eighteen months his stomach had troubled him, his chief complaint being pain there from three to four hours after meals, relieved by taking food. This is considered fairly characteristic of ulcer of the duodenum. Exploration (1919) showed a fixed, but not entirely immovable, mass on the posterior wall of the stomach, much nearer the cardia than the pylorus, causing hour-glass deformity. Gastrogastrostomy (at Walter Reed General Hospital March 14, 1919) brought the patient immediate relief, which was maintained for eighteen months. Secondary nodules became palpable in the liver, and on one occasion the patient vomited some of the tumor, which was shown under the microscope to be adenocarcinoma. Death occurred nine months after operation following a terminal illness of three weeks.

Another man, 52 years old (Jan. 28, 1916), had been under treatment in the medical ward, and (just four weeks after he had been dismissed as "cured" of "ulcer of the stomach") was readmitted to the surgical service with an inoperable carcinoma. This patient, whose gastric symptoms extended over a period of two years, was also relieved by gastrojejunostomy (January, 1916) and returned to his work as a farmer, plowing and reaping all summer; in September he came back with carcinomatous nodules in the otherwise empty sac of an inguinal hernia; he continued to be comfortable so far as his digestion was concerned, until January, 1917, and died in February, thirteen months after operation.

Another patient, a woman, a lawyer, 39 years old (1916), had been complaining of symptoms of the stomach for two years, and during all this time had been under the care of a professor of therapeutics. When he finally asked a surgeon's opinion, exploration (Nov. 18, 1916) showed inoperable carcinoma of the stomach with malignant ascites; death occurred nine weeks after operation.

*Precancerous Lesions.*—We do not wish to engage in the unseemly philippic now raging in the medical journals over the question of ulcer

as a precancerous lesion of the stomach. Alvarez and MacCarty<sup>13</sup> are the authors of the now hackneyed quotation, "Gastric ulcers larger than a quarter (2.4 cm. in diameter) or carcinomas smaller than that are so rarely encountered that the physician with an average practice may go years without seeing one"; and MacCarty's estimate as to the high incidence of precancerous ulcer is well known, even if not acceptable to the majority of his colleagues. The English and continental authorities hold to a more conservative view, as do the majority of our own countrymen, and seem somewhat disinclined to accept all of MacCarty's histologic criteria of malignancy without question. The following two case histories suggest that though the symptoms of gastric ulcer may be relieved by gastrojejunostomy, yet carcinoma can actually develop in the ulcer or in the scar left by its healing.

WARD CASE 3808.—A man, aged 45, on Jan. 15, 1925, complained that for three months he had had constant epigastric pain, aggravated for about two hours after eating. Fifteen years before (1910) he had had a gastrojejunostomy performed elsewhere for ulcer of the stomach, when he was 29 years old. Exploration (1925) showed an inoperable mass on the lesser curvature near the cardia, with metastases to the right lobe of the liver and to the abdominal wall and umbilicus. The gastrojejunal anastomosis did not admit the finger. There was no obstruction to the cardia or the pylorus. Biopsy showed adenocarcinoma with a great increase of fibrous tissue. The patient died four months later. If the cancer had grown at the pylorus, and not at a site where symptoms are so often delayed, the patient might have come to operation early enough for hope of cure. He certainly had had carcinoma for more than three months, and for less than fifteen years.<sup>14</sup>

WARD CASE 3167.—A man, aged 40, on Dec. 18, 1923, complained of stomach trouble for the previous seven weeks. He had been having epigastric trouble for the previous seven weeks. He had been having epigastric cramps.

Eleven years previously (1912), a partial gastrectomy (Polya's) had been done (by Dr. Frazier, in this hospital) for a chronic ulcer on the lesser curvature which showed no evidence of a malignant condition under the microscope. Exploration (1923) showed a fixed inoperable mass on the lesser curvature with metastases to the liver. Death followed in two months. Necropsy was not permitted.

Ulcer is not the only lesion of the stomach held to be precancerous, for, as Miller<sup>15</sup> pointed out, benign polypus and even chronic gastritis

13. Alvarez, W. C., and MacCarty, W. C.: Sizes of Resected Gastric Ulcers and Gastric Carcinomas, *J. A. M. A.* 91:226 (July 28) 1928.

14. Whether or not this carcinoma developed at the site of the former ulcer, perhaps in its scar, is uncertain. But as it is well known that gastrojejunostomy will not prevent the development of an ulcer in the stomach, it is not logical to expect it to heal such a lesion. It is our own firm belief that whenever possible an ulcer of the stomach should be treated by wedge resection or partial gastrectomy. Yet a carcinoma may develop contiguous to, but separate from, a chronic ulcer in the stomach, as in the case of Ernest M., whose history is summarized on pages 338 and 340. Moreover, even after a benign ulcer has been excised, carcinoma may develop after many years (Ward Case 3167).

15. Miller, T. G.: Precursors of Cancer of Stomach, *Pennsylvania M. J.* 34: 170 (Dec.) 1930.

are known to be precursors of malignant growths. Sprunt<sup>16</sup> reported the coexistence in the stomach of tuberculosis and cancer, but carefully avoided any interpretation of the fact.

As we have shown that to rely entirely on symptoms for diagnosis is dangerous practice in gastric cancer, careful physicians and surgeons should take every means to investigate the possibility that their patient's symptoms might be due to carcinoma. The means of diagnosis, aside from symptoms, which have just been discussed, might be classified as follows:

#### I. Purely Clinical Methods

##### (a) Palpable tumor

57 per cent of our cases

60 per cent of Oberniedermayr and Stahnke's series<sup>12</sup>

(A freely movable palpable small tumor is more of a favorable sign than otherwise [Mayo], because it indicates that the growth is accessible.)

##### (b) Cachexia

##### (c) Coffee-ground vomitus

#### II. Laboratory Methods

##### (a) Chemical examination of stomach contents and of stool:

(1) For strength, concentration and type of acid

(2) For occult blood

(Rütimeyer estimates that this finding is positive in 100 per cent of cases; Anschütz, 94 per cent; Boas, 95 per cent<sup>10</sup>).

##### (b) Microscopic examination of stomach contents for abnormal objects

(Oppler-Boas bacilli; fragments of tumor)

##### (c) Roentgen Diagnosis

(A positive roentgen diagnosis is nearly 100 per cent perfect, but a negative is not.)

#### III. Unusual, New and Obsolete Means

##### (a) Gastroscopy

##### (b) Gastrophotography

##### (c) Serum diagnosis

##### (d) Pneumoperitoneum

##### (e) Inflation or distention of the stomach

#### IV. Exploratory Laparotomy

*Exploratory Laparotomy.*—Exploratory laparotomy is sometimes the only means of ascertaining the truth. Nor should other means of diagnosis be persisted in too long, lest the stage of operability (even of palliative operation) pass without the diagnosis being certain. It is true that exploratory laparotomy is not infallible. Among the patients formerly included in the present series with gastric carcinomas were three on whom gastrojejunostomy was done under the impression that

16. Sprunt, D. H.; Carcinoma and Tuberculosis: Report of Case with Review of Literature, Surg., Gynec. & Obst. 51:245 (Aug.) 1930.

the inoperable mass found obstructing the pylorus was carcinomatous; but as these three patients remained in good health more than three years after this palliative operation, they have been removed from the list of patients with cancer and transferred to the group with benign ulcers, thus reducing the number of patients with carcinoma from fifty-seven to fifty-four.<sup>17</sup>

In all other patients the correctness of the diagnosis has been proved either by the lesions found at necropsy, at operation (secondary nodules in liver, etc.), by laboratory examination of the excised specimen or by the patient's death. In a fourth patient, partial gastrectomy was done on a clinical diagnosis of carcinoma, but under the microscope no malignant condition could be found. Including these four patients, later classified as having ulcer instead of carcinoma, there were forty-six patients who, when their abdomens were opened, were thought to be suffering from carcinoma. Four errors in clinical diagnosis among forty-six patients is a percentage of less than 8.7. Certainly no other means of clinical diagnosis is any more accurate than exploratory operation. Furthermore, these errors are not objectionable because they resulted in proper treatment in spite of the error.

*Roentgen Examination.*—Apart from exploratory laparotomy, we believe roentgen study to be the most nearly infallible means of diagnosis (Dr. Ralph S. Bromer and his staff cooperated in the conduct of these studies). Yet many patients were so ill from starvation, and the clinical diagnoses so reasonably certain, that operation was done without the delay of roentgen study. It is interesting to note in passing that the first roentgenogram of the stomach was made in 1896, by an American, John Conrad Hemmeter.<sup>18</sup>

*Gastric Analysis.*—Though many brilliant contributions to pure science and the physiology of digestion have been made on the chemistry of digestion by chemists from the time of the first work by Young<sup>19</sup> in his graduating thesis from the University of Pennsylvania on "An Experimental Inquiry into the Principles of Nutrition and the Digestive

17. Schönbauer and Orator reported the case of one cancerous patient who survived gastro-enterostomy four years, and of another who survived sixteen and one-half years (Wien. klin. Wchnschr. **37**:79, 1924). Daneel recorded one seven year survival after gastro-enterostomy (Results in Gastric Cancer Cases Treated at the Heidelberg Clinic from 1898 to the End of 1905, Beitr. z. klin. Chir. **59**:283, 1908).

18. Hemmeter, J. C., cited by Garrison, F. H.: History of Medicine, ed. 3, Philadelphia, W. B. Saunders Company, 1922, p. 686.

19. Young, John R.: An Experimental Inquiry into the Principles of Nutrition and the Digestive Process, graduating thesis, University of Pennsylvania, 1803; cited by Garrison, pp. 329 and 505.

Process" (1803) through Beaumont<sup>20</sup> to the present, nevertheless, in actual practice we fail to lay as much stress on chemical analysis as some authorities, and can recall no case in which the results of such an analysis outweighed all other considerations. Even the demonstration of lactic acid is regarded as equivocal, as it has been proved to occur in noncancerous conditions.<sup>21</sup>

#### TREATMENT OF CANCER

*No Operation.*—On twelve of our patients no operation was attempted; three patients refused, and in nine it was considered useless to attempt even exploration. Only four of these twelve patients died in the hospital; of the eight discharged, three died within less than seven weeks; one was still living in misery when last heard from, a year later, and four could not be traced.

The average duration of life from the onset of the first symptom is a little over a year (15.7 months in a vast series of cases, 1919-1927, taken in the San Francisco Cancer Survey<sup>22</sup>).

*Operation.*—As was indicated earlier, there have been no known cures after treatment by electricity, light, radiant energy, drugs, chemicals or biologic products. Surgical removal of the lesion, for the present, is the only hope. Although surgery of the stomach has a long history, there being a record of an operation in 1625 on the stomach of a patient who had swallowed a knife,<sup>23</sup> it is only since Billroth's first successful pyloric resection in 1881<sup>24</sup> that carcinoma in this organ has been cured. This brilliant Zürich professor, later of Vienna, heads a famous list of surgeons who distinguished themselves in this field—including his pupil, Johann von Mikulicz-Radecki (the first to use gloves in surgery, cotton ones, later superseded by rubber, introduced by Halsted), Vincenz Czerny, Anton Wölfler (first gastro-enterostomy, 1881), von Haberer, Finsterer and many others throughout the world. One of the reasons why there are no Billroths today is that there are so many of them. Today there are, in widely scattered regions, many surgeons capable of doing, almost as a routine, what was considered most unusual by the pioneers during the evolution of surgery of the stomach.

20. Beaumont, W.: M. Rec. 8:14, 1825; 9:94, 1826; cited by Garrison, F. H., p. 506.

21. Dodds, E. C., and Robertson, J. D.: Lactic Acid and Carcinoma of the Stomach, *Lancet* 1:171 (Jan. 25) 1930; *Quart. J. Med.* 23:175 (Jan.) 1930.

22. Hoffman, F. L.: San Francisco Cancer Survey, 6th Preliminary Report, Newark, N. J., 1931, p. 12.

23. de Lint, J. G.: Operation in 1635 upon Stomach of Patient Who Had Swallowed a Knife, *Æsculape* 20:223 (Aug.) 1930.

24. Billroth, Theodore: *Wien. klin. Wchnschr.* 31:162, 1881.

*Operability.*—If a patient with carcinoma is to be cured he must belong to that class which lends itself to radical operation. In what proportion of patients with gastric cancer is there opportunity of performing a radical operation? The bar diagram in figure 4 shows the proportion, in percentage of the whole number of patients seen, that each type of exploratory, palliative and radical operation bears to the

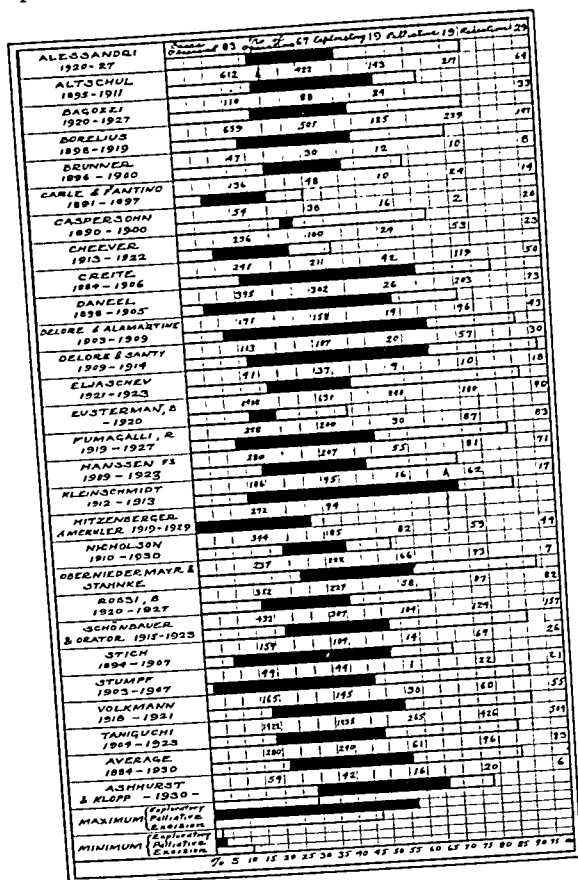


Fig. 4.—The proportion, in percentage, of all patients seen, and of each type of operation for carcinoma of the stomach. The white bar to the left represents exploratory operations; the black bar, palliative operations, and the white bar to the right, resections.

other two, and to the whole number of patients observed by the surgeon (table 1).

Whether or not these percentages are calculated from the whole number of patients seen or merely from those coming to operation makes a significant difference in the result. The wide variation in statistics depends, among other things, on this very influential factor. Careful selection of cases, with exclusion of those thought to be too



TABLE 1.—Data in Cases of Gastric Carcinoma Observed by Various Authorities

Years	Author	No. of Cases Observed	No. of Operations	Per Cent	Ex-plora-tory	Per Cent	Pallia-tive	Per Cent	Resec-tion	Per Cent
1920-1927	Alessandri.....	83	67	81	19	28	19	28	29	43
1914	Alexinski.....	...	...	...	...	...	...	...	297	...
1895-1911	Altschul.....	612	422	69	143	34	217	51	64	15
1924-1926	Balfour.....	...	113	..	48	42	19	16	46	40
1920-1927	Bagozzi.....	110	88	80	24	24	31	35	33	35
1903-1927	Bastianelli, P.....	374	272	73	80	29	95	35	97	36
1928	Bastianelli, R.....	...	543	..	128	23	176	32	293	44
1931	de Beule.....	258	247	96	...	..	51	20	197	79
1878-1890	Billroth.....	...	...	...	...	...	28	..	28	..
1912	Bindsell.....	...	...	...	...	...	38	..	...	..
1898-1919	Borelius.....	659	501	76	125	24	229	45	147	29
1896-1900	Brunner.....	47	30	64	12	40	9	30	10	33
1896-1905	Brunner.....	...	62	..	12	19	32	51	18	29
1891-1897	Carle and Fantino.....	136	48	35	10	20	24	50	14	29
1890-1900	Caspersohn.....	54	38	70	16	42	2	5	20	50
1913-1922	Cheever.....	236	190	42	24	24	53	53	23	23
1884-1906	Creite.....	241	211	88	42	19	119	56	50	23
1900-1920	Crossan.....	80	51	64	17	33	20	39	14	27
1881-1892	Czerny, R.....	...	38	..	9	23	17	44	12	31
1898-1905	Dancel.....	395	302	76	26	8	203	67	73	24
1920	Deaver.....	...	...	...	...	...	...	...	46	..
1903-1909	Delore and Alamartine.....	171	158	92	19	12	96	60	43	27
1904-1914	Delore and Santy.....	113	107	95	20	18	57	53	30	25
1913	Derjushinsky.....	...	146	..	72	49	16	10	58	39
1896-1900	Elselsberg.....	...	...	...	...	...	45	6	22	3
1921-1923	Eljashev.....	41	37	90	9	24	10	27	18	43
1920	Eusterman and Bueerman.....	1,408	631	45	249	38	100	16	290	46
1913	Faroy.....	...	64	..	8	13	39	61	16	25
1912	Feurer.....	...	...	...	...	...	...	...	58	..
1910-1929	Finsterer.....	...	535	..	68	18	70	19	345	65
1927	Frank.....	77	62	80	32	52	9	11	21	34
1919-1927	Fumagalli.....	228	200	88	30	15	87	44	88	41
1913	Galpern.....	...	79	..	14	17	33	41	32	40
1920-1927	Gamerini.....	...	95	..	29	30	40	42	26	27
1912	Gar.....	...	...	...	...	...	...	...	18	..
1878-1894	von Hacker.....	...	...	...	...	...	51	..	42	..
1909-1923	Hanssen.....	280	207	74	55	26	51	39	71	34
1919-1929	Hitzenberger and Merkler.....	272	94	35	...	...	...	...	...	..
1895-1910	Hoffmann.....	...	309	..	55	18	144	46	103	34
1912-1913	Kleinschmidt.....	106	95	90	16	16	62	65	17	17
1911	Güttner.....	...	...	...	...	...	...	...	102	..
1891-1904	Makkas.....	...	458	..	68	14	223	48	163	35
1897-1919	Mayo, O.....	...	2,094	..	746	35	612	29	736	35
1914	Mikaye.....	...	...	...	...	...	...	...	116	..
1893-1895	Mündler.....	...	20	..	5	25	11	56	4	20
1910-1930	Nicholson.....	344	185	54	82	44	59	32	44	24
1911	Nyström (all cases in Sweden in 1911)	...	...	...	...	...	...	...	225	..
1922-1926	Oberniedermayr and Stahnke.....	237	222	94	66	30	73	32	83	37
1887-1926	Persson.....	...	1,150	..	339	29	450	39	361	31
1903	Petersen.....	...	...	...	...	...	...	...	57	..
1928	Puccinelli.....	...	110	..	31	28	29	26	50	45
1908	Ribeira and Sans.....	...	93	..	14	15	50	53	29	31
1920-1927	Rossi, B.....	352	227	65	53	25	87	38	82	23
1920-1927	Rossi, F.....	228	200	88	30	15	87	44	83	41
1915-1923	Schönbauer and Orator.....	432	387	90	104	26	126	32	157	40
1928	Segre.....	...	34	..	3	9	21	62	10	29
1920-1927	Serafini.....	...	70	..	31	44	34	48	5	7
1914	Sherren.....	...	...	...	...	...	...	...	27	..
1895-1897	Steudel.....	...	60	..	8	13	45	75	7	11
1894-1903	Stich.....	159	109	68	14	12	69	63	26	23
1903-1907	Stumpf.....	49	44	90	1	2	22	50	21	47
1904-1923	Taniguchi.....	1,422	1,235	86	265	21	426	34	514	44
1911	Témoin.....	...	336	..	...	...	...	...	25	24
1920-1927	Vecchi.....	...	102	..	23	22	54	52	57	57
1918-1921	Volkmann.....	163	145	89	20	20	60	41	62	51
1929	Walton.....	262	204	78	(132)	65	(132)	65	120	22
1907-1911	Weil.....	445	364	82	128	35	116	30	6	14
1930	Ashhurst and Klopp.....	54	42	78	16	28	20	45	...	...

risky, will reflect itself largely in a favorable influence in the radical operability, as well as in the mortality, statistics. Unfortunately, as will be noted by a glance at table 1, many authors reckon as 100 per cent merely the number of patients operated on and not the total number submitted to their judgment. Balfour,<sup>25</sup> for example, modestly offers this fact, as a partial explanation of the clinic's favorable results in operations for peptic ulcer. Statistics, to be absolutely comparable, should include those patients who refuse operation, or whose condition is inoperable.

The average percentage of patients with carcinoma submitted to resection in the statistics of figure 4 is thirty, with a maximum of forty-six and a minimum of ten. Up to Jan. 1, 1930, out of a series of fifty-four patients with carcinoma of the stomach under the care of the senior author (Dr. Ashhurst), only six (11 per cent) were observed early enough for radical operation. Of these six patients, however, four (66 per cent) have survived their operation for seven years or longer, and may be reckoned as "five year cures":

Benjamin E., aged 43, operated on in 1919; well in April, 1932 (thirteen years).

Ernest M., aged 55, operated on in 1920; well in April, 1932 (twelve years).

Harry W., aged 60, operated on in 1925; well in April, 1932 (seven years).

John D., aged 68, operated on in 1925; well in April, 1932 (seven years).<sup>26</sup>

The results are the same to March, 1933.

The percentage of five year cures reported by surgeons may be distorted in all sorts of ways, as shown in figure 5 and table 2, which are self-explanatory. The important column is the percentage of the total number of patients under observation who obtain five year cures; a high figure in this column is an index of what is called "surgical judgment" (column 2, table 2 and the first bar in figure 5). A comparison of various surgeons' results is most difficult, since some report the percentage of survivors, others the percentage of those appearing in the end-result clinic.

The duration of life among the patients "cured" at least five years is sometimes remarkably long, considering the expectation of life at

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25. Balfour, D. C.: *Proc. Staff Meet., Mayo Clin.* 5:64 (March 5) 1930.

26. A fifth patient, John M., aged 45, who was operated on in 1921, was well in 1930 (nine years); but as there is disagreement between pathologists as to whether or not his lesion (excised from the lesser curvature) is or is not carcinoma, his case is not included. Reports of cures, such as that by Quigley, in which there is no reasonable proof of carcinoma, should be definitely so labeled in their titles (*Three Cured Cases of Supposed Carcinoma of the Stomach*, *Nebraska M. J.* 13:338 [Sept.] 1928).

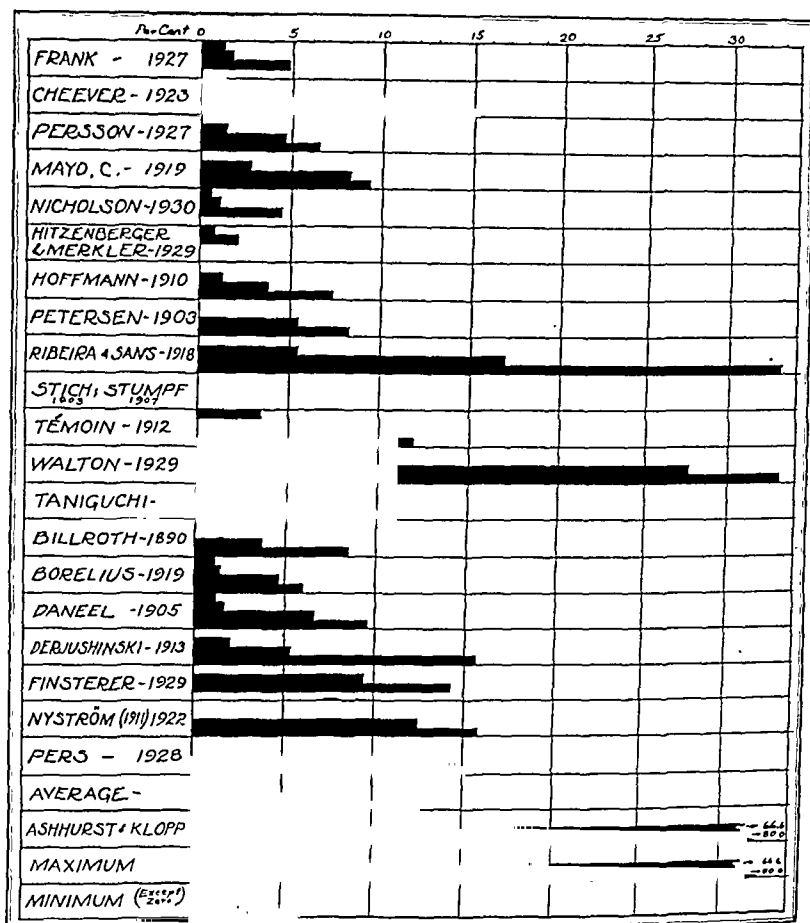


Fig. 5.—Percentage of five year cures. Reading from top to bottom, the first bar represents cures in percentage of all patients; the second bar, in percentage of all operations; the third bar, in percentage of radical operations, and the fourth bar, in percentage of survivors of resections.

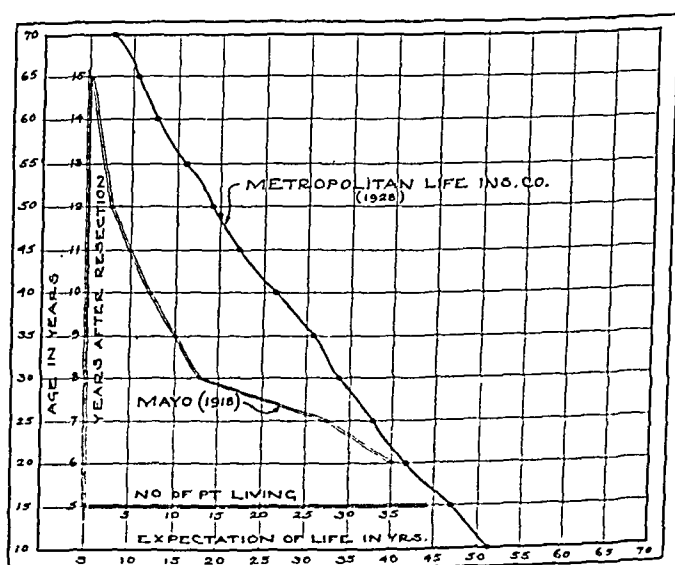


Fig. 6.—Expectation of life curve is plotted in black; the number of patients surviving excision is plotted (double line) against the years after resection.

the average cancer age.<sup>27</sup> (In figure 6 is shown the expectation of life curve drawn from figures of the Metropolitan Life Insurance Company, Industrial Department, 1928, for selected ages between 10 and 70 years.)

*Exploratory Operation.*—As indicated already, exploration was urged on every patient who we thought would survive. Some writers claim that the question of inoperability may be as easily decided by roentgenologic study as by exploration. This has not been our own experience. In spite of a negative roentgen examination, we once

TABLE 2.—Five Year Cures in Cancer of the Stomach

Date	Author	No. of 5 Year Cures	Per Cent of All Patients	Per Cent of All Opera- tions	Per Cent of Radical Opera- tions	Per Cent of Surviv- ors of Resection
1927	Frank.....	1	1.3	1.6	4.8	...
1923	Cheever.....	3	1.3	3.0	13.0	15.0
1910	Paterson.....	..	...	1.4	4.7	6.5
1927	Persson.....	17	...	...	...	...
1918	Mayo, W. J.....	..	...	...	26.0	...
1919	Douglas.....	..	...	...	27.0	...
1928	Pauchet.....	..	...	...	31.3	...
1919	Mayo, C.....	59	...	...	8.1	9.3
1930	Nicholson.....	2	0.58	1.04	4.5	...
1929	Hitzenberger and Merkler.....	2	0.73	2.1	...	...
1910	Hoffmann.....	4	...	1.3	3.9	7.4
1903	Petersen.....	3	...	5.3	...	8.3
1903	Ribeira and Sans.....	5	...	5.4	17.1	33.3
1903	Stich.....	0	0	0	0	0
1907	Stumpf.....	0	0	0	0	0
1923	Taniguchi.....	49	3.5	4.0	9.0	11.1
1911	Témoïn.....	12	3.5	...	12.0	...
1929	Walton.....	33	7.4	9.1	27.5	33.0
1890	Billroth.....	1	...	...	3.6	8.3
1919	Borellus.....	7	1.1	1.4	4.8	6.0
1905	Daneel.....	5	1.3	1.6	6.8	9.6
1913	Derjushinsky.....	3	...	2.0	5.2	15.8
1929	Finsterer.....	50	...	9.3	14.2	...
1922	Nyström.....	28	...	...	12.4	15.8
1930	Deaver.....	2	...	...	...	...
1930	Jones and Scott.....	1	...	...	...	...
1930	Schwyzler.....	1	...	...	...	...
1928	Pers.....	3	...	...	10.0	15.0
1925	Anschütz.....	20	...	...	...	...
1911	Küttner.....	27	...	...	...	...
1915	von Haberer.....	2	...	...	...	...
	Ashhurst and Klopp.....	4	7.4	9.5	66.6	80.0

27. Bloodgood<sup>2a</sup> mentioned a twenty year survival after partial gastrectomy for cancer; Pers, two survivals, of twenty-two and one-half and nineteen and one-half years, respectively (Results Obtained by Resection in Cancer of the Stomach, *Acta chir. Scandinav.* 64:405, 1928); Schwyzler, one of twenty-four years (Cancer of the Stomach: Case Without Recurrence Twenty-Four Years After Operation, *Ann. Surg.* 92:540 [Oct.] 1930), and Weil, two, of nineteen and twenty-one years, respectively (Carcinoma of the Stomach, 1891-1911, *Beitr. z. klin. Chir.* 1115:461, 1919). Of W. J. Mayo's patients (Cancer of Stomach, *Surg., Gynec. & Obst.* 26:367 [April] 1918), thirty-five lived more than six years, with a gradual decline in the total number living, as shown in figure 6, in which the data have been superimposed on an expectation of life curve to show the similarity in shape. Balfour (Curability of Cancer of Stomach, *Surg., Gynec. & Obst.* 54:312 [Feb. 15] 1932) reported from the Mayo Clinic one hundred and twenty-eight patients who lived ten years or more after radical operation. One of our survivors, Benjamin E. is living (April, 1932) at the age of 56, thirteen years after operation.

found a mass of carcinoma (unfortunately inoperable) high in the fundus of the stomach (greater tuberosity). Nor has a positive roentgenologic report, however unfavorable, ever deterred us from opening an abdomen in the hope of being able to do at least a palliative operation. In fact, it may be said that every one of these operations has been commenced as an exploration. Fortunately, in 62 per cent of these explorations it was possible to do either a radical (in 45 per cent of all operations) or a palliative operation (in 48 per cent of all operations), leaving only sixteen patients (38 per cent of the total operations), for whom nothing could be done. (In figure 4 the results of other authorities are compared.)

*Mortality of Exploratory Operation.*—The death rate in these sixteen exploratory operations was high (43.7 per cent), and all patients who survived and were sent home, except one, died in less than five months. The one exception is a man living, in miserable health, one year after exploration, who showed a carcinoma high on the posterior wall of the stomach (fundus) not causing obstruction, but with metastases in the liver.

The cause of death after exploration, whether death occurred while the patient was still in the hospital or after discharge, was attributed to the progress of the disease in every case except one; in the case excepted, pneumonia was the cause, death occurring four days after exploration under ether. If this were the only one to be recorded as a postoperative death, our operative mortality in exploration would fall from 43.7 to 6 per cent, which is nearer the figures given by many surgeons under these circumstances (fig. 7; table 3).

The following anesthetics were used in our exploratory operations:

Ether was used three times with two deaths: one from pneumonia on the fourth day, and the other from the patient's disease, after one week.

Nitrous oxide gas was used twelve times, with four deaths, all from the patient's disease, at intervals from twelve days to six weeks after operation.

Local anesthetic was used once, with death from the patient's disease forty-eight hours later. Perhaps it was an error to have performed an exploratory operation on so ill a patient.

It is our practice to get patients in whom exploration has been done out of bed early after operation, as they easily become bedfast and die.

*Palliative Operation.*—Palliative operation was done on twenty patients, or 30 per cent of the whole number seen, or 48 per cent of those subjected to operation. The operations were as follows: Gastro-jejunosomy (fifteen posterior and one anterior) was done in sixteen

cases for pyloric obstruction. Gastrogastrostomy was performed once for hour-glass obstruction. Gastrostomy was performed in three cases for cardiac obstruction.

The following anesthetics were used in our palliative operations:

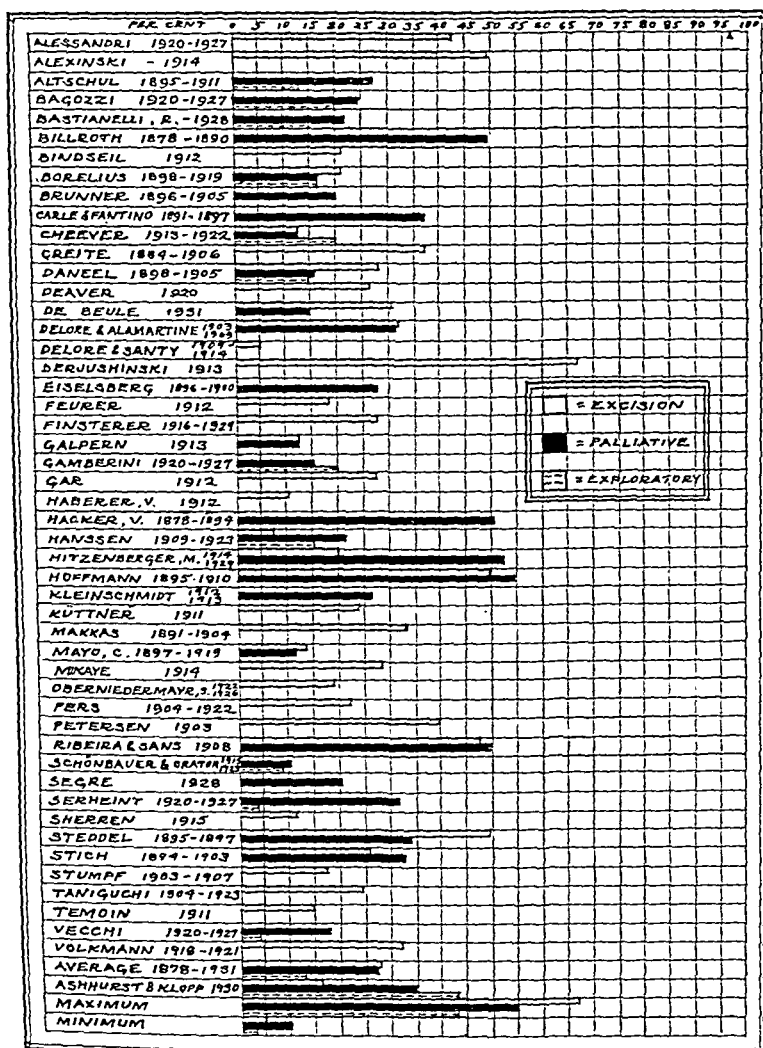


Fig. 7.—Operative mortality in cancer of the stomach for three types of operations.

Ether was used five times, with one death from surgical shock eighteen hours after operation.

Nitrous oxide gas was used eight times, with three deaths: one, after forty-eight hours, from the patient's disease; one, after seventeen days, from multiple pulmonary abscesses, and one, after one month, from progress of the disease.

Local anesthetic was used six times, with three deaths, all within a few days, from asthenia.

Spinal anesthetic was used once, with recovery.

TABLE 3.—*Operative Mortality of Various Types of Operation for Cancer of the Stomach*

Author*	Exploratory Deaths		Palliative Deaths		Resection Deaths	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Alexinski.....	..	..	..	..	148	50
Altschul.....	19	13	54	27	20	40
Bagozzi.....	5	20	8	25	14	42
Bastianelli, P.....	9	11	22	23	21	21
Bastianelli, R.....	..	15	..	21	..	28
de Beule.....	..	..	..	15	..	31
Billroth.....	..	..	14	50	16	56
Bindsell.....	..	..	..	..	8	21
Borelius.....	21	16	38	16	31	21
Brunner.....	8	26	..	..	..	..
Carle and Fantino.....	..	..	9	37	..	..
Caspersohn.....	..	..	..	..	11	55
Cheever.....	5	20	7	13	3	13
Crelte.....	..	..	..	..	19	38
Crossan.....	7	41	10	50	5	36
Dancel.....	4	15	33	16	21	28
Deaver.....	..	..	..	..	12	26
Delore and Alamartine.....	..	..	..	33	14	33
Delore and Santy.....	..	..	..	..	1	5
Derjushinsky.....	..	..	..	..	39	67
Elselsberg.....	..	..	13	28	7	31
Faroy.....	6	..	8	..	7	45
Feurer.....	..	..	..	..	11	19
Finsterer.....	..	..	..	..	..	12
Galpern.....	..	..	..	12	..	7
Gamberini.....	6	20	6	15	2	28
Gar.....	..	..	..	..	5	..
von Hacker.....	..	..	25	50	19	45
Hanssen.....	9	16	16	21	5	7
Hiltzenberger and Merkler.....	..	..	50	..	20	..
Hoffmann.....	27	54	..	..	49	50
Kleinschmidt.....	..	..	12	26	..	24
Küttner.....	..	..	..	..	25	34
Makkas.....	..	..	..	..	57	13.7
Mayo, O.....	22	2.9	67	11.1	..	11
Mikaye.....	..	..	..	..	3	..
Nyström.....	..	..	..	..	46	..
Oberniedermayr and Stahnke.....	..	19% mortality of all operations	..	..	..	27
Persson.....	..	17	..	23	101	40
Petersen.....	..	..	..	..	..	45
Ribeira and Sans.....	..	..	24	50	14	21
Schönbauer and Orator.....	10	9	..	10	33	..
Segre.....	..	..	4	20	..	..
Serafini.....	1	3	10	31	3	11
Sherren.....	..	..	..	..	..	..
Steudel.....	..	..	16	35	7	26
Stich.....	..	..	19	34	2	9
Stumpf.....	..	..	..	..	140	25
Taniguchi.....	..	..	..	..	100	15.5
Témolin.....	..	..	..	..	6	24
Vecchi.....	1	4	10	18	18	32
Volkmann.....	..	..	..	..	31	25
Weil.....	..	..	..	..	1	16.6
Ashhurst and Klopp.....	7	44	7	35	..	..

\* See table 1 for number of operations.

*Mortality of Palliative Operation.*—Our general mortality in palliative operation (35 per cent) is very high (fig. 7; table 3). Of the thirteen patients who survived, the subsequent history is known for eleven; these patients were discharged from the hospital and lived in comfort for periods varying from three to fourteen months before

being incapacitated by their final illness, which usually lasted only a few weeks. The patient who had the shortest period of relief after operation (three months) curiously enough had the longest period of disability (four months) before death. The patient with the longest period of good health (fourteen months) was a man of 77 years at the time of operation; fourteen months later he died suddenly, of angina pectoris, having had entire freedom from gastric symptoms since operation.

Table 4 shows the reasons why no radical operation could be undertaken on these twenty patients.

TABLE 4.—*Palliative Operations*

Name	Age	Nature of Growth	Metastasis	Patient's Condition	Lymph Nodes
Louis S.....	60	Fixed	Liver and pancreas	Poor	++
Charles G.....	52	Entire stomach	0	Fair	++
Lizzie W.....	60	Movable	Liver	Poor	++
Jos. A.....	64	Fixed	Ascites	Poor	+-
Jos. B.....	55	Movable	0	Very bad*	0
Paul K.....	55	Fixed, cardia	0	Fair	0
Louis L.....	63	Fixed	Liver	Poor	-
Julia S.....	45	Fixed	0	Bad	-
Samuel E.....	55	Fixed	Retroperitoneal	Fair	++
Albert L.....	58	Movable	Liver and retroperitoneal	Fair	+-
John W.....	77	Fixed	Retroperitoneal	Fair	+-
Bridget O'D.....	55	Extensive, but movable at pylorus	None	Fair	++
John J.....	60	Fixed	Liver and retroperitoneal	Poor	+-
Peter C.....	58	Fixed, cardia	Retroperitoneal	Fair	0
Freda B.....	60	Fixed	Liver	Fair	+-
George K.....	?	Fixed	Retroperitoneal	Fair	00
Benjamin S.....	79	Fixed	Retroperitoneal	Poor	?
Herbert K.....	46	Fixed, invading colon	Retroperitoneal, ascites	Bad	++
Mary C.....	48	Fixed	Liver and retroperitoneal	Poor	++
Gus S.....	58	Fixed	Retroperitoneal	Fair	++

\* Lost 75 pounds (34.2 Kg.) in last ten weeks.

We believe that palliative operations are worth doing in spite of the high early mortality. As Abernethy said of malignant disease in general, "To forbear to operate is to consign the patient to hopeless misery."

*Radical Operations.*—Only on six patients (less than 11 per cent of those treated) was it possible to attempt radical operation (fig. 4). This small percentage is not due to our selection only of the easiest cases, for partial gastrectomy was attempted in every case in which it was thought the patient would survive.

*Mortality of Partial Gastrectomy.*—One of the six patients died soon; a second died, probably of metastasis to the lung, four and one-half months later, and four are still (April, 1932) <sup>26</sup> living from seven to



thirteen years after operation (fig. 7; table 3). A summary of the records in the cases in which gastrectomy was performed follows:

CASE 1.—Benjamin E., aged 42, was admitted to the hospital on Aug. 2, 1919, and was discharged on October 20. He remained well for thirteen years. Following influenza in 1918, he had never been strong enough to work. His normal weight was 160 pounds (72.6 Kg.). In the three months before admission, it dropped from 144 to 125 pounds (65.3 to 56.7 Kg.). His chief complaint was weakness, loss of appetite and heaviness after eating, relieved by self-induced vomiting. For two months before admission, he had symptoms of pyloric obstruction. Roentgen examination showed retention.

Operation on August 8 (ether) disclosed a movable mass at the pylorus with enlarged lymph nodes in the gastrohepatic and gastrocolic omenta. There was no metastasis to the liver. Partial gastrectomy (fig. 8) was performed.<sup>28</sup>

The patient gained 25 pounds (11.3 Kg.) in three months following operation. The present weight (1932) is about 157 pounds (71.2 Kg.) and the patient has no complaints. He works daily as a clothing finisher. His appetite is normal, and he has no digestive disturbances except a tendency to constipation, relieved by an occasional dose of laxative. The abdominal scar is firm.

Laboratory examination showed a large callous ulcer involving nearly the entire circumference of the stomach. Histologic study revealed adenocarcinoma. The lymph nodes in the gastrohepatic and gastrocolic omenta showed carcinoma. (The patient was presented Oct. 28, 1925, at the meeting of the Clinical Congress of Surgeons in Philadelphia, clinic at the Episcopal Hospital.)

CASE 2.—Ernest M., aged 55 years, referred by Dr. H. M. Freas, was admitted to the hospital on Sept. 28, 1920, and discharged on October 23. He was well for twelve years. He gave a history of indigestion and belching for eighteen months; vomiting for nine months, lately coffee-ground vomitus, and a loss of 50 pounds (22.7 Kg.) in weight. Roentgen examination showed retention of one fourth of the barium sulphate meal after six hours. A mass, probably operable, was seen at the pylorus, with the crater of the original ulcer and a larger surrounding mass of carcinoma.

Operation performed on October 1 (gas and 90 cc. ether) disclosed a mass the size of an ordinary apple in the prepyloric region of the stomach, adherent to the pancreas, causing hour-glass deformity. There was no metastasis to the liver. Partial gastrectomy (Polya's) was performed; dissection of the stomach from the pancreas was difficult. The patient made an uneventful recovery.

He gained 35 pounds (15.9 Kg.) within one year after operation. Twelve years later, at the age of 67, his weight is normal (145 pounds [65.8 Kg.]); he has no digestive disturbances, but eats smaller meals and at shorter intervals than before operation. An occasional laxative is necessary. He works daily as a tool dresser.

Laboratory examination showed chronic perforation of the stomach at the lesser curvature on the posterior wall. Independent and contiguous was a carcinomatous ulcer about 8 cm. in diameter, occupying the entire remaining lumen of the stomach. Histologic study revealed colloid carcinoma of the stomach. No notes were made about the cut ends of the specimen. Gastrohepatic lymph nodes showed carcinoma in the capsule, probably from direct extension. The lymph nodes in

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28. Polya's technic was used. Convalescence was delayed by a bad infection of the abdominal wound, attributed to the neglect of the operators to change their gloves after completing the gastrectomy. The secondary suture of the incision was done on November 21.

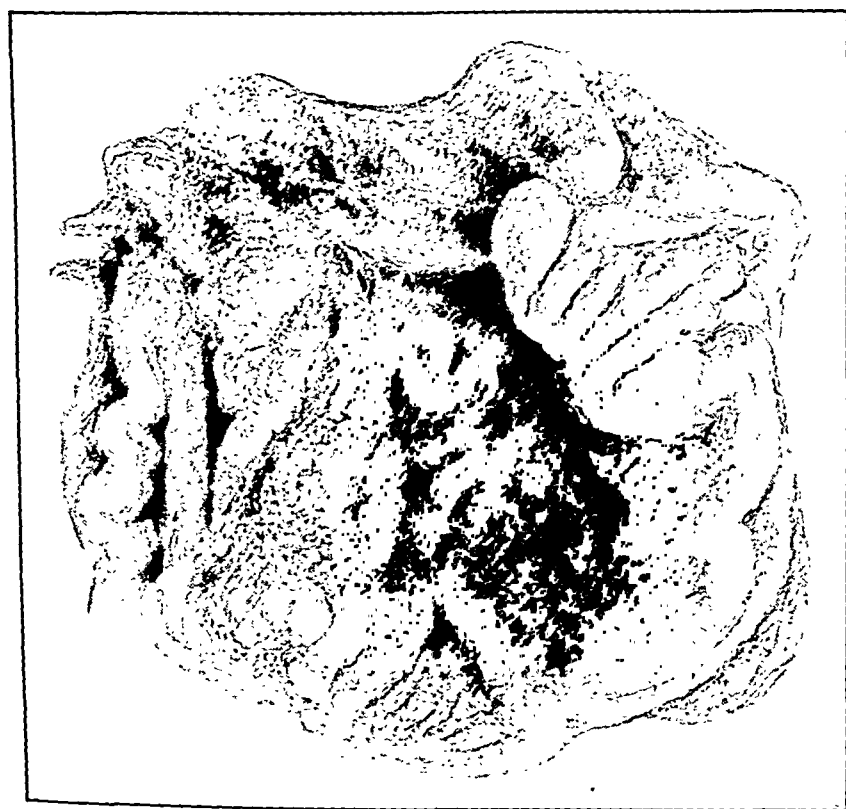
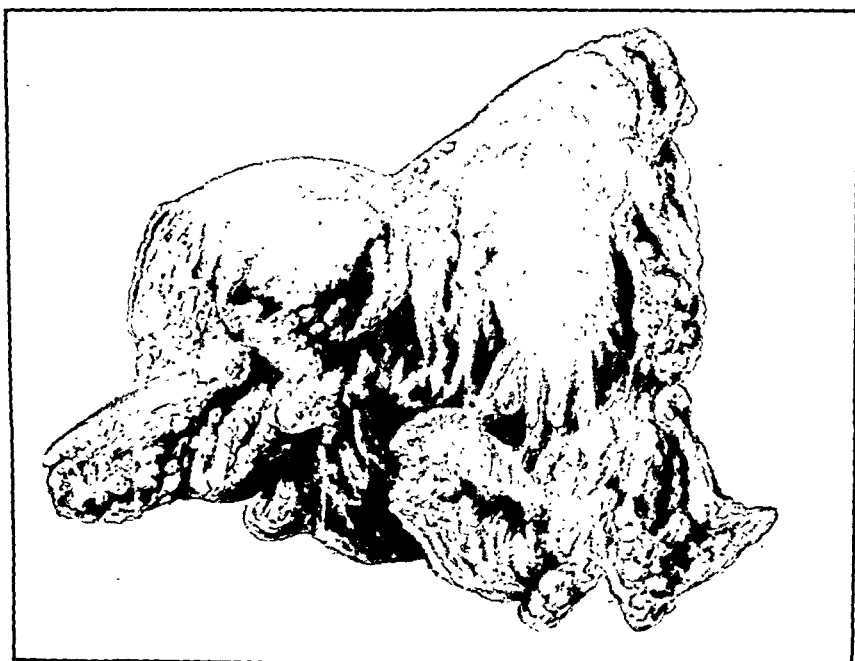


Fig. 8.—Adenocarcinoma of stomach in a man 42 years of age, with invasion of lymph nodes. The specimen (secured by partial gastrectomy in 1919) is shown intact above. In the lower cut the specimen has been opened along the lesser curvature, and the anterior wall of the stomach turned down, exposing ulcerated carcinoma involving almost entire circumference of stomach. The patient (Benjamin E.) was well over thirteen years after operation. (Courtesy of P. Blakiston's Son & Company, Philadelphia.)

the gastrocolic omentum showed doubtful carcinoma. (The patient was presented Oct. 28, 1921, and Oct. 28, 1925, at meetings of the Clinical Congress of Surgeons in Philadelphia, clinic at the Episcopal Hospital.)

CASE 3.—Julia E., aged 65, was admitted to the hospital on Sept. 25, 1921, and died on September 29, forty-eight hours after operation. She complained of vomiting, nausea and loss in weight of 34 pounds (15.4 Kg.) during five or six months. Lately she had frequently vomited coffee-ground material. A roentgenogram was not taken.

Operation on September 27 (gas) disclosed a tumor in the body of the stomach, from one curvature to the other, with enlarged lymph nodes in the gastrohepatic and gastrocolic omenta. No metastasis was found in the liver. Subtotal gastrectomy (Polya's) was performed. The patient had to be catheterized three times after operation, and had gastric lavage three times for vomiting. Death occurred forty-eight hours after operation from asthenia. Necropsy showed anastomosis intact and no peritonitis; metastasis in the right lobe of the liver was not disclosed at operation.

Laboratory examination showed, on the lesser curvature, an ulcer 7 cm. in diameter, circular, with indurated raised walls; the cardiac section was only from 1.5 to 2 cm. from the ulcer; the pyloric section, 5 cm. from the ulcer. Histologic study showed medullary carcinoma. No notes were made on the cut ends of the specimen or on the lymph nodes.

CASE 4.—Mary T., aged 75 years, referred by Dr. R. S. Hooker, was admitted to the hospital on April 12, 1924, and was discharged on April 30. Death occurred four and one-half months after operation. For eight weeks preceding admission, she had epigastric pain, and for the past two or three weeks, vomiting. The normal weight was 145 pounds, but she lost 43 pounds (19.5 Kg.) in eight weeks. A roentgenogram showed retention of three fourths of the opaque meal after six hours, and a filling defect at the pylorus.

Operation performed on April 5, 1924 (gas) disclosed a mass at the pylorus, but no metastasis to the liver. Partial gastrectomy (Polya's) was done. The patient's recovery was uneventful.

The patient was comfortable till a few weeks before death (Aug. 27, 1924), four and one-half months after operation, after an illness characterized by cough and expectoration (probably pulmonary metastasis). No necropsy was performed.

The specimen measured 12 cm. on the lesser curvature and 15 cm. on the greater curvature; the duodenal end passed 2 or 3 cm. beyond the gross lesion, and the cardiac end, 5 or 6 cm. Histologic study revealed adenocarcinoma; lymph nodes in both the gastrohepatic and gastrocolic omenta showed early carcinoma; the pyloric cut end of the specimen showed carcinoma; the cardiac cut end showed no carcinoma.

CASE 5.—Harry W., aged 60, was admitted to the hospital on Jan. 7, 1925, and was discharged on March 6. He was well for seven years. The chief complaint was pain after eating for five months previous to admission, relieved by vomiting. He had lost 23 pounds (10.4 Kg.) in weight. A roentgenogram showed retention of one sixth of the barium sulphate meal after six hours; there was a filling defect in the prepyloric region, probably from adhesions; "if a carcinoma it was probably small and operable."

Operation performed on January 19 (gas) disclosed a freely movable mass at the pylorus; there was no metastasis to the liver; enlarged lymph nodes were seen in the gastrohepatic and gastrocolic omenta. Partial gastrectomy (Polya's) was done. Recovery was complicated by persistent hiccup from Jan. 23 to 31, 1925. One stitch abscess developed.

The patient was in good health in April, 1932, seven years after operation.

The operative specimen measured 11 cm. on the lesser curvature, and 16 cm. on the greater curvature. There was an annular carcinoma at the pylorus. The pyloric section passed 2 cm. distant from the gross lesion, but a record concerning the cardiac end was lost. Histologic examination showed adenocarcinoma. The cardiac cut end showed freedom from carcinoma. The gastrocolic omentum lymph nodes and one lymph node from the gastrohepatic omentum showed carcinoma.

CASE 6.—John D., aged 68 years, was admitted to the hospital on Feb. 10, 1925, and discharged on March 16. He was well for seven years. For six months he had constant gnawing pain in the epigastrium, beginning one or two hours after meals, which was sometimes relieved by eating. Lately he had belching and small amounts of vomitus and lost 25 pounds (11.3 Kg.). A roentgenogram showed a filling defect at the pylorus, but no obstruction.

Operation performed on February 11 (gas) disclosed a movable mass at the pylorus; there was no metastasis to the liver; the lymph nodes beneath the pylorus and in the gastrocolic omentum were enlarged. Partial gastrectomy (Polya's) was performed, followed by an uneventful recovery. Seven years later, in April, 1932, the patient, then aged 75, was well, except for the feebleness of age. A roentgenogram (January, 1930) showed no carcinoma in the stomach; no obstruction at anastomosis, and a shadow in the lung suspected of being due to metastasis. Clinically, there were no symptoms or physical signs of a pulmonary lesion as late as April 15, 1932.

The specimen measured 10.5 cm. on the lesser curvature, and 18.5 cm. on the greater. Histologic examination showed adenocarcinoma; both cardiac and pyloric cut ends of the specimen showed carcinoma.<sup>29</sup>

Lymph nodes in both the gastrohepatic and gastrocolic omenta showed carcinoma.

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29. I have reviewed the slides of this specimen, and I can find none which shows this at the cut ends. The slides found show, in my opinion, freedom from carcinoma or any question of carcinoma at the cardiac and pyloric sections (J. W. K.).

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# LYMPHATIC DRAINAGE OF JOINTS

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Very little is known concerning the lymphatic drainage of joints, although much has been written about the lymphatics of the other serous cavities. In the textbooks on anatomy, and even in the larger atlases, one rarely finds mention of lymphatics in joint cavities. The normal physiology of the lymphatics draining joint cavities and the functional disturbances which they manifest in disease are understood even less clearly. Since the discovery of lymphatic vessels by Asellius in 1622, many studies have been made to determine their presence and distribution in various parts of the body, but little has been learned of their function. The study of articular lymphatics was neglected until interest was aroused in the complex anatomy and physiology of the joints.

The study and dissection of the lymphatics by early investigators<sup>1</sup> led them to conclude that there were two channels of lymphatic drainage in the limbs, a deep and a superficial trunk. The superficial trunk in the lower extremity accompanied the great saphenous vein and was believed to drain all the tissues above the superficial muscular fascia, into the popliteal and inguinal lymph nodes. The deep trunk in the lower extremity followed the femoral vein and drained the tissues beneath the superficial fascia into the popliteal, deep femoral and iliac lymph nodes. In the upper extremity the superficial trunk followed the cephalic and basilic veins to the deep cubital nodes, to the lateral axillary and to the deep pectoral and infraclavicular nodes. The deep trunk followed the deep blood vessels to the deep cubital and axillary lymph nodes. Until recently it was believed that deep and superficial lymphatic systems had no intercommunication until they united along the femoral or external iliac vein in the lower extremity or in the axilla in the upper extremity. Baum,<sup>2</sup> however, in 1925 demonstrated lymphatics piercing the superficial muscular fascia in the horse, apparently uniting the deep and superficial systems. Miller,<sup>3</sup> in 1919, observed lymphatics in the lung between the pleural and parenchymal systems which functioned as anastomoses in cases of obstruction. Previously,

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1. Hewson, W.: *Experimental Inquiries on the Lymphatic System*, London, J. Johnson, 1774.

2. Baum, H.: *Ztschr. f. Anat. u. Entwcklgsgesch.* **77**:266, 1925.

3. Miller, W. S.: *Am. Rev. Tuberc.* **3**:193, 1919.



these two systems in the lung had been considered wholly separate. The present conception seems to be that while intercommunications do exist between the deep and superficial lymphatic systems in the extremities, normally these systems function as separate entities.

The first studies of the lymphatics were made by observing the absorption of fat through the lacteals of the intestinal tract after the feeding of fat to animals. A little later attempts were made to make injections directly into the lymphatics. Retrograde injections with metallic mercury were made after tying off the thoracic duct. By this method the larger trunks only were shown, since rupture of the lymphatic wall soon occurred under the pressure of the material injected. Teichmann,<sup>4</sup> in 1861, was able to show only large lymphatic vessels in the lower extremity by retrograde injections of metallic mercury. Lee<sup>5</sup> found that retrograde injections were possible for only a few centimeters after ligation of the thoracic duct in cats. John Hunter<sup>6</sup> was particularly skilful in this method, and many of his specimens are still to be seen in the museum of the University of Glasgow.

Direct injections into the lymphatics in the direction of the lymph flow have always been extremely difficult. The small lymphatic vessels could not be found readily and attempts at injection with colored solutions soon ruptured the thin lymphatic wall. Florey and Carleton<sup>7</sup> have recently reported direct injections into the smaller lymphatics of the diaphragm with a fine glass pipet. They found that rupture of the lymphatic capillary occurred at 2.5 cm. of water pressure. In attempts to make injections into the lymphatic vessels at their entrance to lymph nodes, I was able to obtain an injection for only a few inches before the lymphatic vessel ruptured. Under normal conditions, in retrograde injections the lymphatic vessel wall ruptured before the valves within the lymphatic vessel became incompetent.

These difficulties in the demonstration of lymphatic vessels by direct injection led to attempts to make injections into them indirectly. It was found by Bowditch,<sup>8</sup> in 1873, that lymphatics could be traced fairly well by injecting dyes mixed with turpentine directly into thin sheets of tissue. Gerota,<sup>9</sup> in 1896, with a similar method was able to trace lymphatics for a short distance by injections directly into the tissues of

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4. Teichmann, L.: *Elephantiasis of Lymphatic Vessels*, Kraków, 1892; *Das Säugetier-system von anatomische Standpunkt*, Leipzig, Wilhelm Engelmann, 1861.

5. Lee, F. C.: *Bull. Johns Hopkins Hosp.* **33**:21, 1922.

6. Hunter, J., quoted by Reichert, F. L.: *The Regeneration of the Lymphatics*, *Arch. Surg.* **13**:871 (Dec.) 1926.

7. Florey, H., and Carleton, H. M.: *Brit. J. Exper. Path.* **8**:479, 1927.

8. Bowditch, H. P.: *The Lymph Spaces in Fascia: A New Method of Investigation*, Boston, D. Clapp & Son, 1873.

9. Gerota, D.: *Anat. Anz.* **12**:35 and 216, 1896.

animals immediately after death. With the technic described by Gerota, Hermann Baum<sup>10</sup> has made an exhaustive study of the lymphatic system, particularly in cattle and horses. Injections of dyes directly into the tissues have been used in recent studies on the lymphatics by Henderson,<sup>11</sup> Hashiba,<sup>12</sup> Higgins,<sup>13</sup> Dewey and Noyes,<sup>14</sup> Mouchet,<sup>15</sup> Brain,<sup>16</sup> Josseffoff,<sup>17</sup> Horton<sup>18</sup> and Rienhoff.<sup>19</sup>

These methods, while giving a fairly satisfactory picture of the lymphatic distribution, have failed to show clearly the finest ramifications. To correct this fault in the older methods, Magnus,<sup>20</sup> in 1922, devised a method for showing the finer lymphatics by the use of hydrogen dioxide. He found that when hydrogen dioxide was brought in contact with living tissues the lymphatic vessels became filled with oxygen gas, owing to a catalytic action of the lymph on the hydrogen dioxide. To a slight extent the blood vessels also became dilated, but the investigators who have used this method, Rostock,<sup>21</sup> Stubel<sup>22</sup> and Magnus,<sup>23</sup> have found that this was a negligible factor, since the blood vessels could be easily differentiated from the lymphatics. This method was found useful for small sections of tissue which were studied microscopically with either transmitted or reflected light. Recently, Brown,<sup>24</sup> Fisher<sup>25</sup> and Rynearson<sup>26</sup> have studied lymphatics by using dilute solutions of colloidal silver. The colloidal silver in very dilute solution was injected directly into a serous cavity, from which it was taken up by macrophages and carried into the lymphatics. After several hours the

10. Baum, H.: *Das Lymphgefäß-system des Rindes*, Berlin, A. Hirschwald, 1917; *Anat. Anz.* **63**:122, 1927; *Deutsche tierärztl. Wchnschr.* **35**:413, 1927.

11. Henderson, R. W.: *Anat. Rec.* **16**:319, 1919.

12. Hashiba, G. K.: *Anat. Rec.* **12**:331, 1915.

13. Higgins, G. M.: *Anat. Rec.* **30**:243, 1925.

14. Dewey, K. W., and Noyes, F. B.: *The Lymphatics of the Dental Region*, J. A. M. A. **71**:1179 (Oct. 12) 1918; *Publ. Dept. Anat. Univ. Illinois*, 1917, vol. 4, no. 2.

15. Mouchet, A.: *J. de l'anat. et physiol.* **45**:433, 1909.

16. Brian, F. V.: *Ann. d'anat. path.* **6**:1253, 1929.

17. Josseffoff, J. M.: *Anat. Anz.* **69**:213, 1930.

18. Horton, B. T.: *Pyloric Block: With Special Reference to the Musculature, Myenteric Plexus and Lymphatic Vessels*, *Arch. Surg.* **22**:438 (March) 1931.

19. Rienhoff, W. F., Jr.: *The Lymphatic Vessels of the Thyroid Gland in the Dog and in Man*, *Arch. Surg.* **23**:783 (Nov.) 1931.

20. Magnus, G.: *Deutsche Ztschr. f. Chir.* **175**:147, 1922.

21. Rostock, P.: *Beitr. z. klin. Chir.* **175**:147, 1926.

22. Stubel, A.: *Virchows Arch. f. path. Anat.* **244**:287, 1923.

23. Magnus, G.: *Deutsche Ztschr. f. Chir.* **210**:307, 1928.

24. Brown, K. P.: *Brit. J. Surg.* **15**:538, 1928.

25. Fisher, A. G. T.: *Chronic Non-Tuberculous Arthritis*, New York, The Macmillan Company, 1929.

26. Rynearson, E. H.: *Proc. Staff Meet., Mayo Clin.* **3**:171, 1928.

tissue lining the serous cavity was removed and studied microscopically by transmitted light. The lymphatic vessels were then seen as tiny, brown-filled channels coursing through the tissues.

While methods of demonstration were still rather crude, a number of important findings were made in regard to the lymphatics of the joints and bones. Ludwig and Schwagger-Seidel,<sup>27</sup> about 1870, injected colored substances into joints, and reported the absence of lymphatics in the synovial membrane and the joint capsule. Budge,<sup>28</sup> in 1873, working with cats, found a rich network of lymphatics in the periosteum, substantia compacta and marrow cavity of bone, but he made no mention of lymphatics about the joints. The first demonstrations of lymphatic vessels in articular structures were made by Tillmans<sup>29</sup> in 1876. A solution of Berlin blue was injected into the knee joint of a dog that had just been killed, by a hole bored through the femoral condyle. By alternately flexing and extending the lower leg for one hour, he was able to show blue dye in the synovial membrane and in lymphatic vessels almost to the middle of the thigh. Later, working with larger joints (horse and ox knee joints), he made injections directly into the synovial membrane. Here he found a deep and a superficial layer of lymphatic vessels, a dense plexus just beneath the serous coat of the synovial membrane and a smaller number of lymphatic vessels near the bones or ligaments to which the synovial membrane was attached. Magnus<sup>30</sup> described a similar arrangement of lymphatic vessels in the capsules of joints. Lymphatics in the synovial membrane were also demonstrated by Baum<sup>31</sup> after the direct injection of dyes into the capsules of joints.

#### EXPERIMENTAL DATA

The study reported in this article was begun five years ago in an attempt to find out the nature of the joint lymphatics in the lower extremity and their drainage, and, then, any possible relationship of lymphatic drainage to arthritis. In the early part of this work india ink in 10 per cent gelatin, prussian blue in 10 per cent gelatin and Gerota's mixture of prussian blue in turpentine and ether were used. Injections were made into the deep or the superficial tissues of the lower extremities soon after the death of animals that had been used for other lines of research; dogs, cats, rabbits and guinea-pigs were used. When the injection mass was injected into the subcutaneous tissues, it could be traced along the superficial blood vessels to the popliteal, inguinal and iliac

27. Ludwig and Schwagger-Seidel, quoted by Schdanow, D. A.: *Anat. Anz.* 69:194, 1930.

28. Budge, A.: *Arch. f. mikr. Anat.* 13:87, 1877.

29. Tillmans, H.: *Arch. f. mikr. Anat.* 12:649, 1876.

30. Magnus, G.: *Deutsche Ztschr. f. Chir.* 182:325, 1923.

31. Baum, H.: *Deutsche Ztschr. f. Chir.* 195:241, 1927.

lymph nodes. When the injection was made under the deep muscular fascia, the substance could be traced in the lower leg to the popliteal and lumbar lymph nodes, but it was never found in the inguinal nodes. Attempts were made to show lymphatic drainage by the x-rays. Dilute suspensions of barium (Hill<sup>32</sup>) and brominized lard oil (Putnam<sup>33</sup>) were used. Although in these experiments deposition of the injected material was shown in a few of the lymph nodes on microscopic examination, the lymphatic vessels could not be demonstrated in x-ray films.

These aforementioned methods were of necessity crude. The dye was forced into tissue spaces, and the trauma may have ruptured a number of the smaller lymphatics into which the injected mass then passed, although the recent work of Drinker and Field<sup>34</sup> offers another explanation which will be considered later. Such injections into tissues or articular cavities of dead animals did not give satisfactory demonstrations of the lymphatics. The anatomists who have used this method obtained an adequate portrayal of the lymphatics only by studying a very large number of specimens, each of which showed some one phase, from which a composite picture of the drainage was secured.

After these preliminary attempts to gain familiarity with the methods and technic, injections of india ink were made directly into the joints of living animals. Young adult animals were used. Light ether anesthesia was given in order to prevent extravasation of the ink into periarticular structures, a common error, if the animal moved while the injection was being given. Injections of india ink into the tibioastragalar joint were made in six rabbits. The lymphatic drainage was traced through the so-called deep system to the popliteal and to the external and common iliac lymph nodes.

RABBIT 1.—Light ether anesthesia was given. The hair was shaved about the right ankle, and the skin was painted with 3 per cent iodine. The usual aseptic technic was followed. With a 25 gage needle, 0.25 cc. of india ink (diluted with an equal volume of distilled water) was injected into the right ankle joint on its anterolateral aspect. The animal was killed with chloroform five days later. There was no extravasation of ink in the subcutaneous tissues about the ankle. The ankle joint was deeply stained with ink. One lymphatic vessel was traceable along the posterior tibial vein almost to the middle of the tibia. The popliteal lymph node was stained a deep black from the india ink; no staining was observable in the inguinal lymph nodes. The lymph nodes along the common iliac and external iliac vessels were moderately stained with india ink. No lymph nodes along the inferior vena cava, beneath the diaphragm or in the mediastinal cavity showed any deposition of ink. Sections were taken from the capsule of the joint and from the lymph nodes mentioned for microscopic study.

32. Hill, E. C.: Bull. Johns Hopkins Hosp. **35**:218, 1921.

33. Putnam, T. J.: Some Brominized Oils for Radiographic Use, J. A. M. A. **87**:1102 (Oct. 2) 1926.

34. Drinker, C. K., and Field, M. E.: Am. J. Physiol. **97**:32, 1931.

RABBIT 2.—This animal was discarded because of marked extravasation of india ink into the subcutaneous tissues. There was moderate staining of the popliteal, inguinal and iliac lymph nodes.

RABBIT 3.—The technic was the same as for rabbit 1; 0.25 cc. of india ink was injected into the left ankle joint. The animal was killed in four days. There was no extravasation about the ankle joint. The ankle joint cavity was stained a deep black. No lymphatic vessels were seen about the ankle joint. The popliteal lymph node was deeply stained by the india ink. There was no visible absorption of ink in the inguinal nodes. There was a moderate amount of india ink in the iliac lymph nodes. Sections were taken from the capsule of the joint. The popliteal, inguinal and common iliac lymph nodes were removed for further study.

RABBIT 4.—The technic was the same as for rabbit 1; 0.25 cc. of india ink was injected into the left ankle joint. The rabbit was killed five days after the injection. There was slight extravasation of india ink about the ankle joint. A small lymphatic vessel could be traced from the fibular side of the left ankle joint to the middle of the calf. The popliteal lymph node was deeply stained. There was no evidence of absorption of india ink in the inguinal lymph nodes. There was a moderate absorption of india ink in the external iliac and in the common iliac lymph nodes. Tissue was taken from the capsule of the joint and from the popliteal, inguinal, iliac and subdiaphragmatic lymph nodes for histologic study.

RABBIT 5.—The technic was the same as for rabbit 1; 0.25 cc. of india ink was injected into the right ankle joint. The rabbit was killed three days after the injection. No extravasation was seen about the ankle joint. Some ink was found in the posterior compartment of the joint. The popliteal lymph node was black with india ink. One small lymphatic vessel could be traced downward for about one-half inch (1.27 cm.) from the popliteal lymph node. The inguinal lymph nodes showed no absorption of india ink. There was a slight amount of india ink in the iliac lymph nodes. There was no evidence of absorption in the more proximal lymph nodes. Sections were taken from the capsule of the joint and from the popliteal, inguinal, iliac, epigastric and mediastinal lymph nodes for microscopic study.

RABBIT 6.—The same technic was used as for rabbit 1; 0.25 cc. of india ink was injected into the right ankle joint. The animal was killed four days later. There was no extravasation of the india ink. Much ink was seen in the posterior part of the ankle joint. The popliteal lymph nodes were much blackened from the india ink. No lymphatic vessels were seen. The inguinal lymph nodes showed no evidence of absorption of ink. A moderate amount of ink was seen in the common iliac lymph nodes. There was no evidence of absorption in any more proximal lymph nodes. Tissue was taken from the capsule of the joint and from the popliteal, inguinal and common iliac lymph nodes for study.

After injections into the ankle joints no limitation of motion was noticed in any of the animals after the first day. There was apparently a rapid absorption of the ink from the articular cavity. The ink was found in largest amount about the posterior margin of the ankle joint. This space is less constricted by overlying tendons, which, apparently, play the chief rôle in moving intra-articular substances to various parts of the ankle joint. As a rule, the particles of ink were scattered fairly

uniformly throughout the subserous synovial tissues in the microscopic sections. Phagocytic cells loaded with particulate matter were seen in one section in a lymphatic capillary. No phagocytosis by cells lining the synovial cavity was observed. In some cases there was a slight polymorphonuclear infiltration of the synovial tissues. There was occasional, scattered, lymphocytic infiltration about the blood vessels and in the tissues when the animals lived more than several days (fig. 1).

The popliteal lymph nodes showed many of the lymph sinuses packed with phagocytic cells filled with india ink. There was a tendency for the particulate matter to become concentrated in the germinal center of the lymph node. This became more marked the longer the animal was permitted to live. There were some free particles in the lymph spaces, apparently from the cells that had disintegrated. The lymph nodes did not suggest any evidence of inflammation or venous congestion. None of the inguinal lymph nodes showed any absorption of the india ink. The external and common iliac lymph nodes showed only scattered groups of phagocytic cells filled with ink. The amount that they contained was always greater in the animals living a longer number of days after injection. No absorption of india ink was found in any lymph nodes above the bifurcation of the aorta. The other tissues comprising the reticulo-endothelial system, such as the liver, spleen and bone marrow, were not studied. Key<sup>35</sup> and others have found dyes in the liver, spleen and bone marrow after injection into articular cavities.

In order to determine whether there would be any alteration in the lymphatic drainage, the popliteal lymph nodes, the chief draining reservoir of the ankle joint, were removed from two rabbits.

RABBIT 1.—Ether anesthesia was given, with the usual aseptic technic. Through a midline incision in the popliteal space, the popliteal lymph nodes on the right side were removed. The skin and superficial tissues were closed with silk sutures; 0.25 cc. of india ink was then injected into the right ankle joint. The animal was killed four days later. Dissection showed that all lymph nodes had been removed from the popliteal space. The ankle joint showed no extravasation of the ink. The capsule of the joint was deeply stained, and there was a large amount of the ink in the posterior part of the ankle joint. There was no absorption of ink in the inguinal lymph nodes. The common iliac lymph nodes were deeply stained with ink. There was no evidence of absorption of the ink in any more proximal lymph nodes. Sections of the capsule of the joint and of the inguinal and iliac lymph nodes were removed for microscopic study, which confirmed the macroscopic findings. There was no ink in the microscopic section of the inguinal lymph nodes. There was a large amount of ink in the sections from the external and common iliac lymph nodes.

RABBIT 2.—The technic was the same as for rabbit 1. The left popliteal lymph nodes were removed. This was followed by the injection of 0.25 cc. of ink into the left ankle joint. Three days later the animal was killed. There was

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35. Key, J. A.: *J. Bone & Joint Surg.* 8:666, 1926.

no extravasation about the ankle joint. There was a moderate amount of india ink, particularly in the posterior part of the ankle joint. Dissection showed that the popliteal lymphoid tissue had been completely removed. No lymphatic vessels were seen. The inguinal lymph nodes showed no india ink. The common iliac

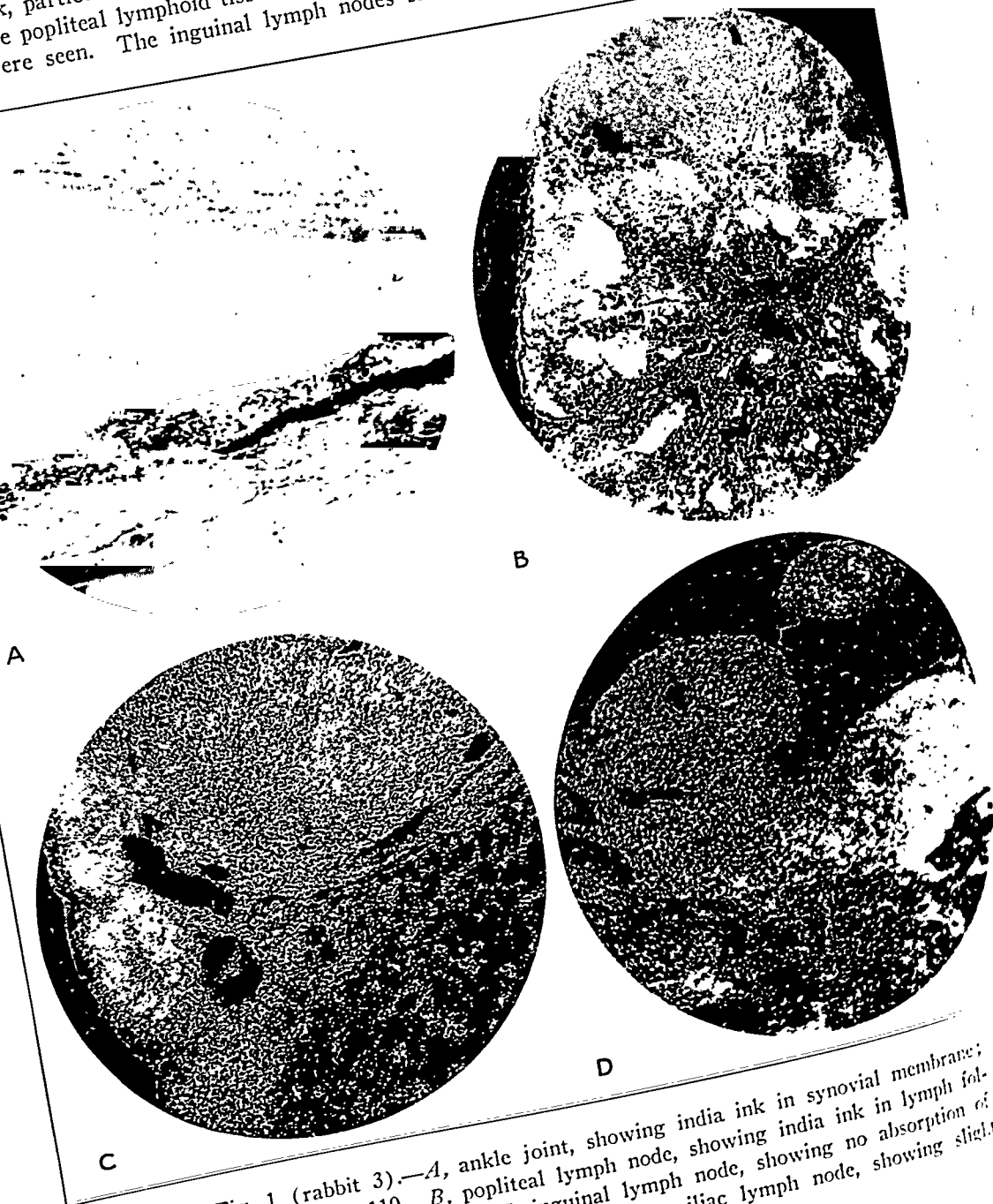


Fig. 1 (rabbit 3).—*A*, ankle joint, showing india ink in synovial membrane; reduced from  $\times 110$ . *B*, popliteal lymph node, showing india ink in lymph follicles; reduced from  $\times 70$ . *C*, inguinal lymph node, showing no absorption of india ink; reduced from  $\times 70$ . *D*, common iliac lymph node, showing slight absorption of india ink; reduced from  $\times 70$ .

lymph nodes were deeply stained with ink. No ink was found in any higher lymph nodes. The microscopic observations were the same as in rabbit 1.

Such experimental removal of lymph nodes is of doubtful value. Krause<sup>36</sup> observed the growth of lymphatics in newly formed tissue, in 1863. Sabin,<sup>37</sup> in 1916, reported that lymphatics regenerate slowly from their endothelial walls after injury. Reichert,<sup>38</sup> in 1926, showed in dogs that the superficial lymphatics regenerated in about four days and the deep lymphatics in eight days. Wocksmuth,<sup>39</sup> Baum<sup>40</sup> and Meyer<sup>41</sup> found, after the extirpation of lymph nodes, that the lymphatic drainage through the area was reestablished, although no regeneration of the lymph nodes occurred. In the animals used in this study, when the popliteal nodes were removed, the drainage passed on to the external iliac lymph nodes, the next proximal lymph nodes of the deep system in the rabbit draining the ankle joint. In such cases the iliac lymph nodes were as deeply stained by the india ink as the popliteal lymph nodes had been in the previous series of rabbits. Reports have appeared in the literature (Hirsch<sup>42</sup> and Cadenat<sup>43</sup>), in which removal or fibroses of lymph nodes led to elephantiasis or swelling of the extremity.<sup>44</sup> However, as Halsted<sup>45</sup> showed in elephantiasis of the arm, Homans and Zollinger<sup>44</sup> in phlegmasia alba dolens and Davis<sup>46</sup> in genital elephantiasis, an associated phlebitis was necessary to produce the condition.

In six rabbits injections of india ink were made directly into the knee joint. In these animals the lymphatic drainage was forced through the so-called deep system to the external and common iliac lymph nodes (fig. 2).

RABBIT 1.—Ether anesthesia was used. The hair over the right knee was shaved, and the skin was painted with alcohol and iodine. The usual aseptic technic was followed; 0.4 cc. of india ink was injected into the right knee joint. Four days later the animal was killed. There was deep staining of the synovial membrane. There was no evidence of absorption into the popliteal lymph node. The inguinal lymph nodes showed no evidence of the ink. The external and common iliac lymph nodes were deeply stained. A lymphatic vessel could be traced from the joint through Hunter's canal almost to the middle of the thigh. No lymph nodes above the common iliac lymph nodes showed any absorption of

36. Krause: *Deutsche Klin.* **15**:377, 1863.

37. Sabin, F. R.: *Harvey Lectures, 1915-1916*, Philadelphia, J. B. Lippincott Company, 1917, p. 124.

38. Reichert, F. L.: *The Regeneration of the Lymphatics*, *Arch. Surg.* **13**:871 (Dec.) 1926.

39. Wocksmuth, W.: *Deutsche Ztschr. f. Chir.* **208**:1, 1928.

40. Baum, H.: *Deutsche Ztschr. f. Chir.* **195**:241, 1926.

41. Meyer, A. W.: *Bull. Johns Hopkins Hosp.* **17**:185, 1906.

42. Hirsch, F.: *Deutsche med. Wchnschr.* **52**:1339, 1926.

43. Cadenat, F. M.: *Bull. et mém. Soc. nat. de chir.* **56**:1184, 1930.

44. Homans, J., and Zollinger, R.: *Experimental Thrombophlebitis and Lymphatic Obstruction of the Lower Limb: A Preliminary Report*, *Arch. Surg.* **18**:992 (April) 1929.

45. Halsted, W. S.: *Bull. Johns Hopkins Hosp.* **32**:309, 1921.

46. Davis, D. M.: *Ann. Surg.* **92**:400, 1930.



india ink. Sections were taken from the joint capsule and from the popliteal, inguinal and external iliac lymph nodes for study.

RABBIT 2.—The technic was the same as for rabbit 1; 0.4 cc. of india ink was injected into the left knee joint. There was slight swelling of the knee, but no

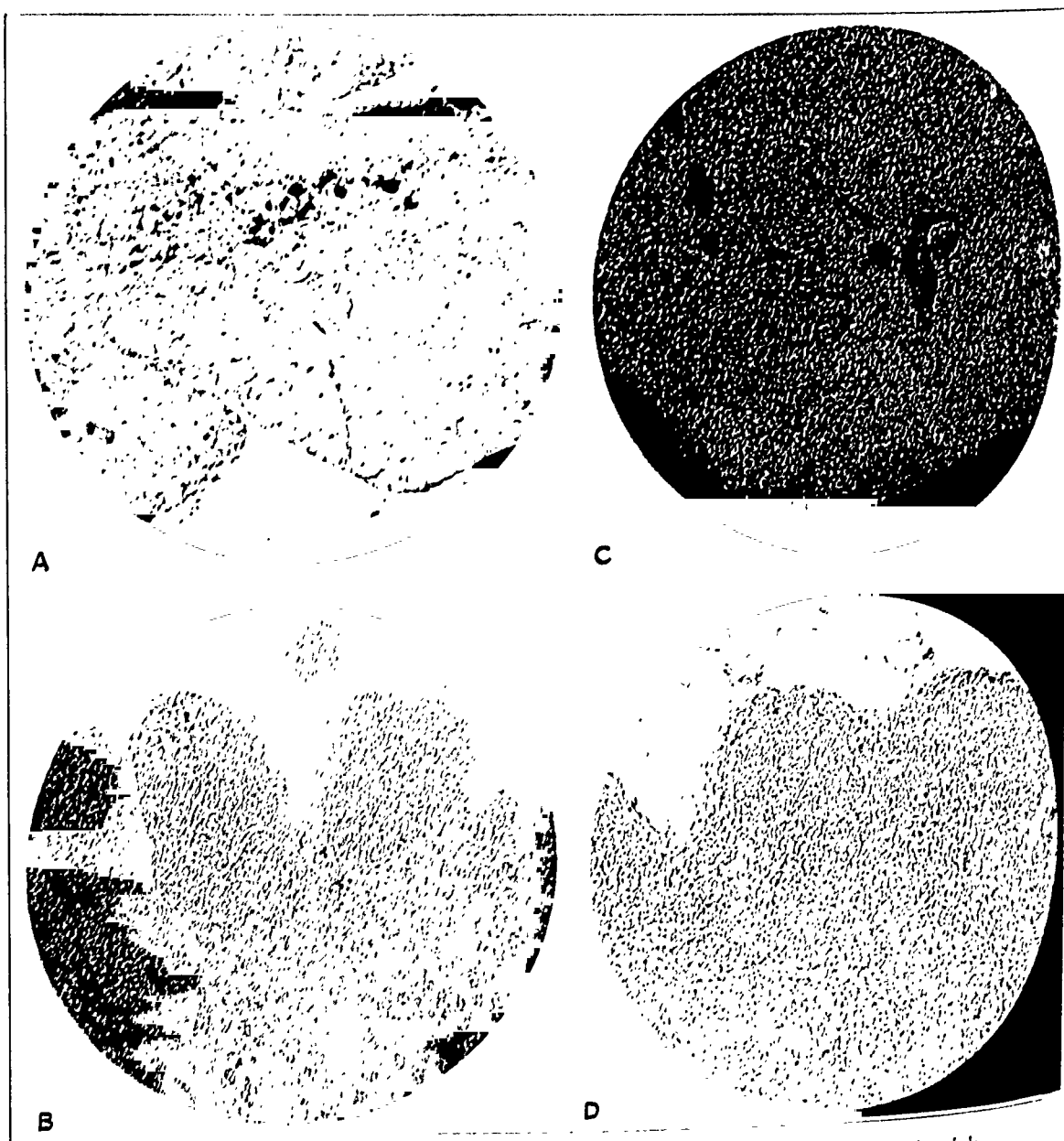


Fig. 2 (rabbit 4).—*A*, portion of joint capsule and fat pad of knee, showing ink in synovial membrane, with some in lymphatic vessels; reduced from  $\times 125$ ; *B*, external iliac lymph node, showing absorption of india ink; reduced from  $\times 80$ . *C*, popliteal lymph node, which shows no absorption of india ink;  $\times 80$ . *D*, inguinal lymph node with no india ink;  $\times 80$ .

noticeable disturbance of function. The animal was killed three days later. No extravasation was seen about the knee joint. There was no evidence of india ink

in the popliteal lymph nodes or the inguinal lymph nodes. No lymphatic vessels were seen. The external and common iliac lymph nodes were deeply stained with ink. Sections were taken from the joint and from the popliteal, inguinal and common iliac lymph nodes for study.

RABBIT 3.—The technic was the same as for rabbit 1; 0.4 cc. of india ink was injected into the left knee joint. There was slight swelling of the knee joint, which passed off in four days. There was no apparent disturbance of function. The animal was killed three days later. There was no extravasation about the joint. The cavity of the joint was stained throughout with india ink. Much india ink still remained in the joint, partly enmeshed in fibrin. The ink was in greatest amount in the quadriceps pouches. There was no evidence of absorption of ink in the popliteal lymph node. Two lymphatic vessels were seen on the surface of the capsule of the joint on the outer side of knee, but these could not be traced farther. The inguinal lymph nodes showed no ink. The external and common iliac lymph nodes were moderately stained with ink. No ink was observed in any more proximal lymph nodes. Sections were taken from the articular capsule and from the popliteal and common iliac lymph nodes for study.

RABBIT 4.—The same technic was used as for rabbit 1; 0.4 cc. of india ink was injected into the right knee joint. There was swelling of the right knee, which was still present when the animal was killed in four days. There was a slight increase in the fluid in the right knee joint. There was slight extravasation of ink on the outer side of the joint. A moderate amount of india ink remained in the knee joint, chiefly in the quadriceps pouches. One lymphatic vessel could be seen going from the posterior aspect of the joint capsule into Hunter's canal. The popliteal lymph nodes showed a little absorption of ink. The external and common iliac lymph nodes showed a moderate absorption of ink. No more proximal lymph nodes showed absorption of ink. Sections were taken from the capsule of the joint and from the popliteal, inguinal and iliac lymph nodes for study.

RABBIT 5.—The technic was the same as for rabbit 1; 0.4 cc. of india ink was injected into the left knee joint. There was a slight swelling of the joint, which lasted for three days. There was no apparent disturbance in function. The animal was killed seven days later. No extravasation of ink was seen about the joint. The knee joint contained a moderate amount of ink, chiefly in the quadriceps pouches. No lymphatic vessels were seen. There was no evidence of absorption of ink in the popliteal lymph nodes or the inguinal lymph nodes. There was a moderate amount of india ink in the external iliac lymph nodes. No ink was found in any more proximal lymph nodes. Sections were taken from the capsule of the joint and from the popliteal, inguinal and external iliac lymph nodes for study.

RABBIT 6.—The technic was the same as for rabbit 1; 0.4 cc. of india ink was injected into the right knee joint. There was a little swelling of the knee joint, which subsided in two days. There was no observable disturbance in function. The rabbit was killed six days later. There was a very slight extravasation into the tissues on the outer side of the knee. The popliteal lymph nodes showed no evidence of absorption of ink. No lymphatic vessels were seen. There was no evidence of india ink in the inguinal lymph nodes. There was a large amount of ink in the external and common iliac lymph nodes. No absorption was seen in any more proximal lymph nodes. Sections were taken from the articular capsule and from the popliteal, inguinal and external iliac nodes for study.

In these animals the drainage of the india ink through the lymphatics could be traced to the external iliac and to the common iliac lymph

nodes (fig. 2). No ink was found in any instance in the inguinal lymph nodes. India ink was found in the popliteal lymph nodes only when there was extensive extravasation. Occasionally lymphatic vessels were seen going from the joint capsule along the geniculate arteries and veins into Hunter's canal. In the articular capsule the india ink was found chiefly on the epithelial surface of the synovial membrane, partly enmeshed in fibrin. Occasional lymph vessels filled with ink-containing phagocytes were seen. Fewer phagocytic cells and ink particles, as well as lymphatic vessels, were seen in the depth of the synovial tissues as one approached their bony or ligamentous attachments. The ink was seen in the lymph nodes in similar arrangement to that described for the ankle joint (fig. 2).

In five rabbits, injections of india ink were made directly into the cavity of the hip joint.

**RABBIT 1.**—Ether anesthesia was used. The hair was shaved from the right groin, and the area painted with alcohol and with 3 per cent iodine. With a 25 gage needle, 0.25 cc. of india ink was injected into the hip joint just external to the femoral artery after the location of the femoral head had been palpated. A moderate amount of limitation in motion of the hip joint was observed for about two days. The rabbit was killed four days later. There was slight extravasation into the muscles. A small amount of india ink was seen in the hip joint along the side of the femoral neck. No lymphatic vessels were seen. There was no evidence of ink in the inguinal lymph nodes. The common iliac lymph nodes were moderately stained with ink. No ink was observed in any more proximal lymph nodes. Sections were taken from the capsule of the joint and from the inguinal and common iliac lymph nodes for study.

**RABBIT 2.**—The technic was the same as for rabbit 1; 0.25 cc. of india ink was injected into the right hip joint. No disturbance in the use of the hip joint was seen. The animal was killed six days later. There was slight extravasation of ink in the deep muscles anterior to the hip joint. No lymphatic vessels were seen. No absorption of ink was seen in the inguinal lymph nodes. There was a moderate amount of deposition of ink in the external and common iliac lymph nodes. No ink was seen in any more proximal lymph nodes. Sections were taken from the capsule of the joint and from the inguinal and iliac lymph nodes for microscopic study.

**RABBIT 3.**—The technic was the same as for rabbit 1; 0.25 cc. of india ink was injected into the right hip joint. No disturbance in the use of the hip joint was seen. The animal was killed six days later. Slight extravasation of ink was seen in the deep muscles anterior to the hip joint. No lymphatic vessels were seen. No absorption of ink was seen in the inguinal lymph nodes. There was a moderate amount of deposition of ink in the external and common iliac lymph nodes. Sections were taken from the capsule of the joint and from the inguinal and iliac lymph nodes for study.

**RABBIT 4.**—Paraldehyde anesthesia was used. The right gluteal region was shaved and painted with alcohol and iodine. Through the posterior approach to the hip joint described by Ober,<sup>47</sup> the capsule of the hip joint was exposed.

47. Ober, F. R.: Posterior Anthrotomy of the Hip Joint, *J. A. M. A.* **83**:1500 (Nov. 8) 1924.

Twenty-five hundredths cubic centimeter of india ink was injected into the hip joint. The limitation in the use of the hip joint had not disappeared in five days, when the animal was killed. There was very slight extravasation of ink into the subgluteal fat. A few lymphatic vessels were seen on the posterior aspect of the joint capsule, but they could not be traced farther. No ink was seen in the inguinal lymph nodes. There was moderate staining of the external and common iliac lymph nodes. No more proximal lymph nodes showed any absorption of ink. Sections were taken from the common iliac and the inguinal lymph nodes and from the articular capsule for study.

RABBIT 5.—Paraldehyde anesthesia was given. The technic was the same as for rabbit 4; 0.25 cc. of india ink was injected into the hip joint posteriorly. There was marked limitation of motion in the joint, but no definite swelling could be palpated. The animal was killed in four days. There was slight extravasation of the ink outside of the capsule of the joint. No lymphatic vessels were seen. There was no india ink in the inguinal lymph nodes. There was a moderate amount of ink in the external and common iliac lymph nodes. No ink was found in any more proximal lymph nodes. Tissue was removed from the joint capsule and from the inguinal and the common iliac lymph nodes for microscopic study (fig. 3).

These experiments showed that the lymphatic absorption from the hip joint in the rabbit was through the so-called deep system to the iliac lymph nodes. In no case was there any absorption into the inguinal lymph nodes. The microscopic study of tissue showed the same manner of absorption of india ink as was seen for the knee and ankle joints. The hip joint being so deeply placed and covered by muscles, the slight extravasation that invariably occurred on injection did not lead to any absorption of india ink by the superficial lymph channels.

A number of clinical observations have been recorded, and I have observed a swelling of the superficial inguinal glands in inflammation of the joints of the lower extremity. Usually such swelling was bilateral, and frequently epitrochlear, axillary and cervical lymph nodes were palpable at the same time. As possible explanations for this, extension of the inflammation to superficial tissues or an involvement of the lymph nodes through a generalized infection of the blood stream has been suggested. Both these experiments and the work of others on the human cadaver have offered no other explanation.

While this work was in progress, several observations on lymphatic drainage of joints appeared in the literature. Baum,<sup>48</sup> in 1927, reported lymphatics in the synovial membrane of dogs after the direct injection of dyes. In the foreleg of the horse he traced the lymphatic drainage from the carpal joints to the cubital (epitrochlear) and cervical lymph nodes; from the elbow joint, lymphatic drainage was traced to the cubital and axillary nodes, and from the shoulder joint, the lymphatic

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48. Baum, H.: *Ztschr. f. d. ges. Anat. (Abt. 1)* 84:192, 1927.

drainage was followed to the axillary, posterior cervical and superficial cervical lymph nodes. At almost the same time Kolodny<sup>49</sup> described the lymphatic drainage of the long bones of the lower extremity after the injection of india ink into dogs. He found that the lymphatic drainage from the bones was entirely through the so-called deep system, to the deep femoral and iliac lymph nodes. In 1929, Smith and Campbell,<sup>50</sup> using berlin blue, a soluble dye, found that the lymphatics were not filled until intra-articular pressure was so great that the joint became greatly distended. They were able to trace lymphatics into Hunter's canal. During the same year, Oschkaderow<sup>51</sup> studied the lymphatics in the interphalangeal joints in cadavers. In these joints he found from three to five lymphatic vessels which joined larger lymphatics along the digital arteries. These lymphatics had no relationship with the fascial spaces of the hand.

Schdanow<sup>52</sup> has recently described the lymphatic drainage of the tarsal, knee and hip joint as observed in the cadavers of stillborn babies. In the tarsal joints he observed lymphatic drainage along the peroneal and anterior tibial vessels to the popliteal lymph node. He did not trace this drainage farther. He found a very complex lymphatic system draining the cavity of the knee joint. The lymphatic radicals were traced along the geniculate vessels into Hunter's canal. He found slight drainage into the popliteal lymph nodes from the posterior and inferior portions of the capsule of the joint. The chief lymphatic absorption, however, was to the deep femoral and iliac lymph nodes. From the cavity of the hip joint he was able to trace lymphatic drainage to the deep femoral and iliac lymph nodes. He observed several very small lymph nodes along the gluteal arteries.

The findings of these investigators were similar to those I found in the rabbit. The lymphatic drainage of joints was found to be through the so-called deep system to the lymph nodes draining this deep system. Job,<sup>53</sup> as well as other students of comparative anatomy, has shown that as a rule the larger and more highly developed animals have more lymph nodes, man having supposedly the greatest number and distribution. In dogs and in man there are femoral nodes draining the deep system, apparently not connected with the inguinal group of lymph nodes. The rabbit does not have deep femoral lymph nodes.

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49. Kolodny, A.: The Relation of the Bone Marrow to the Lymphatic System. Its Rôle in the Spreading of Carcinomatous Metastases Throughout the Skeleton, *Arch. Surg.* **11**:690 (Nov.) 1925.

50. Smith, M., and Campbell, J. R.: *Proc. Soc. Exper. Biol. & Med.* **26**:395, 1929.

51. Oschkaderow, W. T.: *Anat. Anz.* **66**:377, 1929.

52. Schdanow, D. A.: *Anat. Anz.* **69**:194, 1930.

53. Job, T. T.: *Am. J. Anat.* **31**:125, 1922.

An attempt was then made to confirm these findings in regard to lymphatic drainage by studying the absorption of bacteria from joint cavities. Tubercle bacilli were chosen as being the most easily demonstrable.

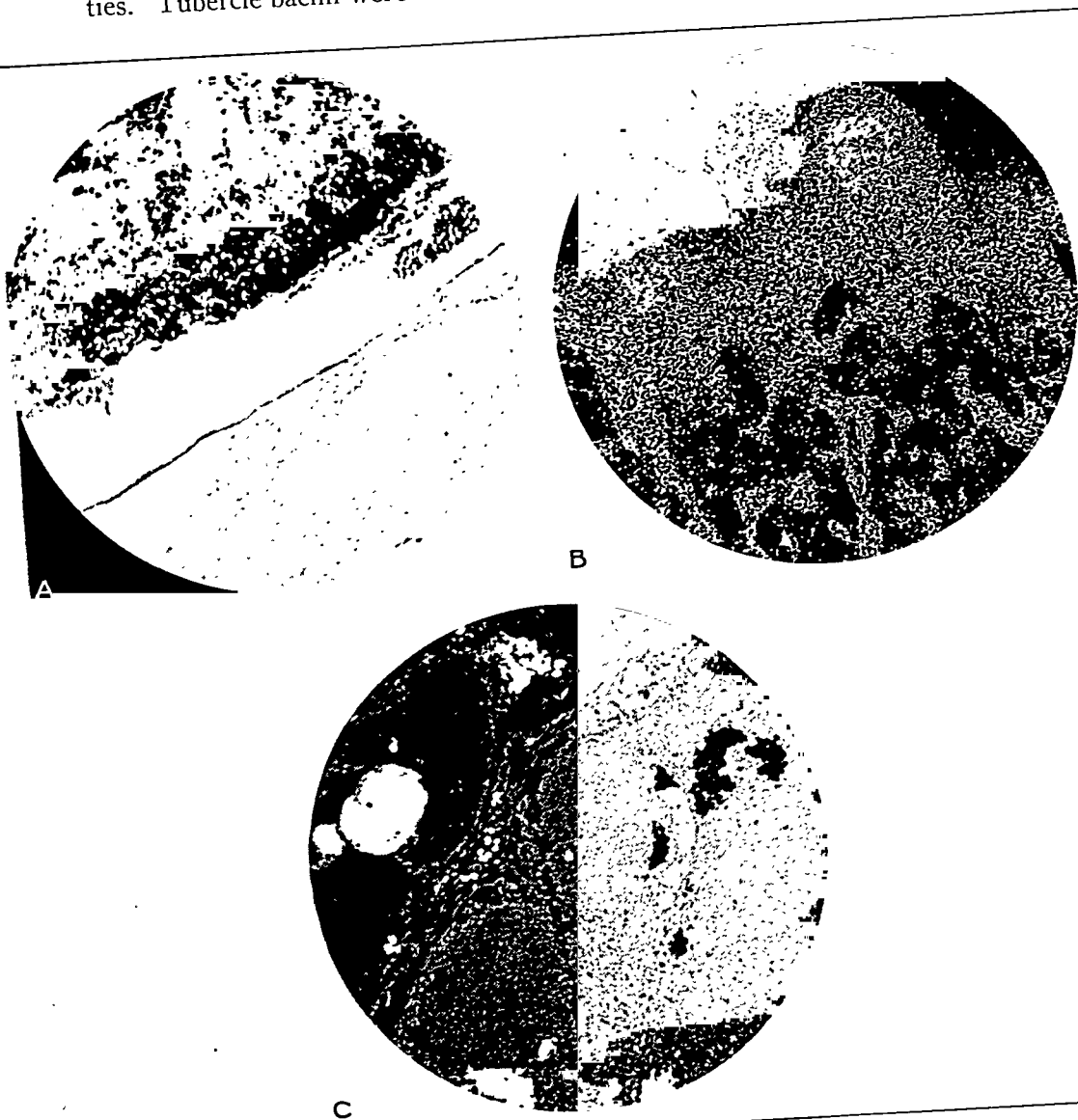


Fig. 3 (rabbit 5).—*A*, india ink in the articular capsule along the neck of the femur; reduced from  $\times 88$ . *B*, inguinal lymph node, showing two rather dense lymphoid follicles but no ink absorption. *C*, common iliac lymph node, showing a moderate amount of india ink. At the left of the lymph node there is a large mass of ink-containing phagocytes in the afferent lymphatic vessel.

Injections of a freshly autoclaved emulsion of human tubercle bacillus (strain H 37) were made into the knee joints of four rabbits.

RABBIT 1.—Ether anesthesia was used. The skin over the right knee was shaved and painted with alcohol and iodine; 0.3 cc. of an emulsion of human tubercle bacilli (strain H 37), freshly prepared and autoclaved, was injected into the right knee joint. There was a little swelling of the knee joint, which had almost subsided when the animal was killed three days later. There was no increase in joint fluid. No tubercle bacilli were found in smears from the joint fluid. Sections were taken from the capsule of the joint and from the common iliac lymph nodes for microscopic study.

RABBIT 2.—The technic was the same as for rabbit 1; 0.3 cc. of a freshly prepared and autoclaved emulsion of human tubercle bacilli was injected into the left knee joint. There were slight swelling and limitation of motion in the knee joint, which disappeared in three days. The animal was killed five days later. There was a slight increase in the joint fluid. No tubercle bacilli were found in smears from the joint fluid. Sections were taken from the capsule of the joint and from the external iliac lymph nodes for study.

RABBIT 3.—The technic was the same as for rabbit 1; 0.3 cc. of a freshly prepared, autoclaved emulsion of human tubercle bacilli was injected into the left knee joint. There were slight swelling in the knee joint and slight stiffness, which disappeared in two days. The animal was killed eight days later. No tubercle bacilli were found in smears from the synovial fluid. Sections were taken from the capsule of the joint and from the common iliac lymph nodes for microscopic study.

RABBIT 4.—The technic was the same as for rabbit 1; 0.3 cc. of a freshly prepared, autoclaved emulsion of human tubercle bacilli was injected into the right knee joint. There was slight swelling of the joint, which disappeared in three days. There was no obvious disturbance in joint function. The rabbit was killed two weeks later. There was no excess fluid in the joint. No tubercle bacilli were found in smears from the joint fluid. Sections were taken from the articular capsule and from the common iliac lymph nodes for microscopic study.

It was supposed that bacilli would be removed from the joints in the same manner as insoluble particles, particularly if the bacteria did not arouse a violent inflammatory reaction. Numerous workers, using guinea-pigs, had recovered tubercle bacilli from the regional lymph nodes after the injection of tuberculous material. Tubercle bacilli found in tuberculous glands of the neck were traced in some cases to tuberculous tonsils. Herring and MacNaughton,<sup>54</sup> from their studies on lymphatics, came to the conclusion that both particulate matter and tubercle bacilli were removed in the same manner by the lymphatics in the human lung. Consequently, it was surprising to find no tubercle bacilli in the articular capsule and in the external and common iliac lymph nodes in any of the rabbits given injections. Microscopic sections examined by several pathologists showed no tubercle bacilli or early tubercle formation (fig. 4). In sections from the right common iliac lymph node in rabbit 4, there was a moderate area of necrosis. However, it could not be determined whether this was due to the mate-

54. Herring, P. T., and MacNaughton, F. G.: *Lancet* 1:1081, 1922.

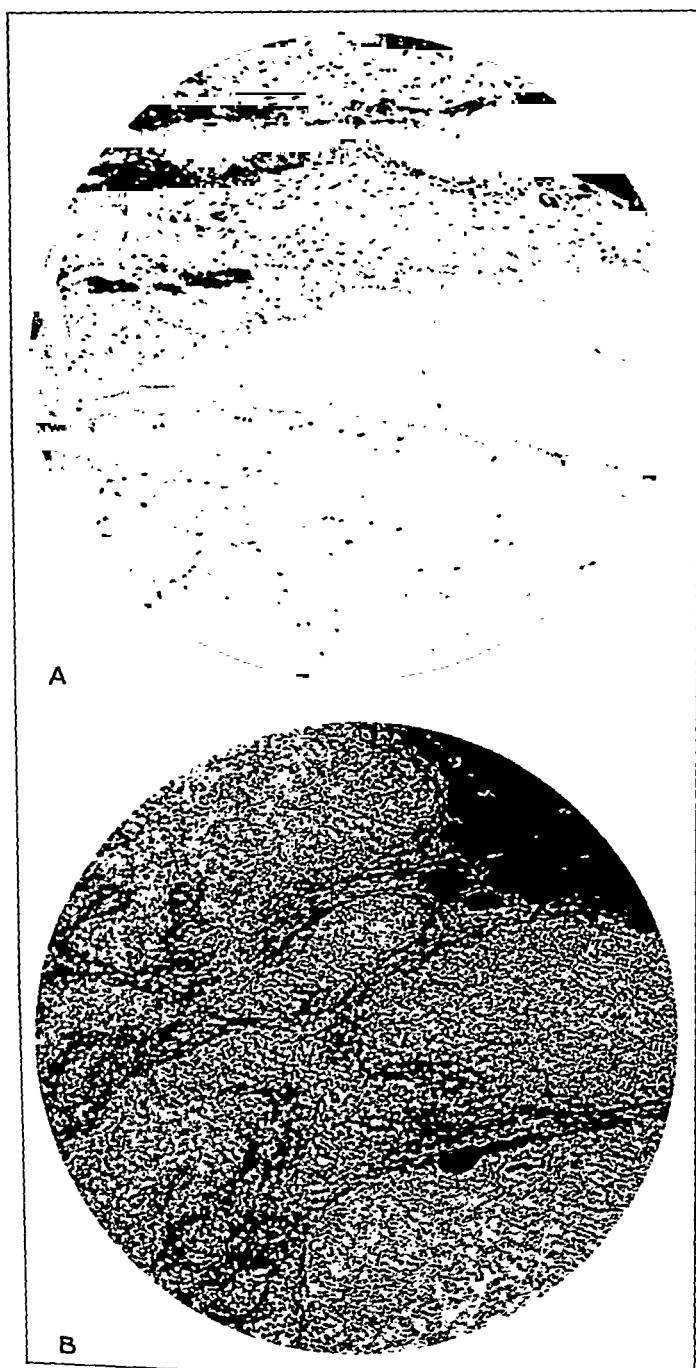


Fig. 4 (rabbit 4).—*A*, synovial villus and cartilage. There is no evidence of tuberculous disease or of inflammation;  $\times 78$ . *B*, common iliac lymph node, no tuberculosis;  $\times 90$ .



rial injected. Because no bacilli were found in the joint tissues or lymphatic system, it was thought that the bovine type of bacilli might give better results, since rabbits are supposed to be relatively resistant to human tubercle bacilli. Again, the autoclaving might have made it possible for the joint and tissue fluids to bring about a more rapid disintegration of the tubercle bacilli.

Consequently, an emulsion of a rapidly growing colony of bovine tubercle bacilli, smears of which showed as many as 20 bacilli per oil immersion field, was injected into the knee joints of two rabbits. This emulsion was not autoclaved.

RABBIT 1.—The technic was the same as for the rabbits of the previous series; 0.3 cc. of a freshly prepared emulsion of living bovine tubercle bacilli was injected into the right knee joint. There was slight swelling and stiffness, which had not subsided when the animal was killed three days later. There was a little increase in joint fluid. Smears from the joint showed no tubercle bacilli. Sections were taken from the joint capsule and from the right common iliac lymph node for study.

RABBIT 2.—The technic was the same as for rabbit 1; 0.3 cc. of a freshly prepared emulsion of living bovine tubercle bacilli was injected into the right knee joint. There was slight swelling, which subsided in two days, but no obvious disturbance of function. The rabbit was killed two weeks later. There was no increase in joint fluid. The joint had the usual macroscopic appearance. No tubercle bacilli were found in the joint fluid. Sections were taken from the joint capsule and from the right common iliac lymph node for microscopic study.

Again, no tubercle bacilli were found either in the articular capsule or in the common iliac lymph nodes. Nor did the capsule of the joint or the lymph nodes show any evidence of a tuberculous infection. The tubercle bacilli that had been injected had disappeared in some inexplicable manner. It was decided to repeat the work. This time the bovine tubercle bacilli were stained *in vitro* by the Ziehl-Neelsen method, washed, centrifugated and taken up again in salt solution before injection. Samples of the suspension showed as many as 10 tubercle bacilli per oil immersion field. This emulsion was injected into the ankle joint in two rabbits and into the knee joint in two rabbits.

RABBIT 1.—The usual aseptic technic was used; 0.25 cc. of the emulsion of bovine tubercle bacilli which had been stained *in vitro* was injected into the right ankle joint. The animal was killed four days later. Examination of the ankle joint showed a slight increase in fluid, but no evidence of the injected material. Tissue from the articular capsule and from the right external iliac lymph nodes was removed for microscopic study.

RABBIT 2.—The technic was the same as for rabbit 1; 0.25 cc. of an emulsion of stained bovine tubercle bacilli was injected into the left ankle joint. Except for slight swelling, which disappeared in three days, no local reaction was noted. The animal was killed eight days later. No bacilli were seen in smears from the joint fluid. Tissue was removed from the joint capsule and from the iliac lymph nodes for histologic examination.

RABBIT 3.—The technic was the same as for rabbit 1; 0.5 cc. of an emulsion of stained tubercle bacilli was injected into the left knee joint. There was slight swelling in the joint for three days, but no other joint reaction. The animal was killed eight days later. There was no evidence of tubercle bacilli in the joint. Sections of the articular capsule and the common iliac lymph nodes were removed for microscopic study.

RABBIT 4.—The technic was the same as for rabbit 1; 0.5 cc. of an emulsion of stained bovine tubercle bacilli was injected into the left knee joint. There was slight swelling of the knee, which disappeared in three days. The animal was killed two weeks later. The knee joint showed a slight inflammatory reaction. There was no evidence of tubercle bacilli in the joint fluid. Sections were taken from the joint capsule and from the iliac lymph nodes for microscopic study.

It was thought that the lymphatic absorption of bacilli described by Willis,<sup>55</sup> Miller<sup>3</sup> and Herring and MacNaughton<sup>54</sup> might be observed better by first staining the tubercle bacilli in vitro by the Ziehl-Neelsen method. This technic had been used by a number of investigators working with tuberculosis. Cultures of bovine bacilli grown on Petroff's medium were scraped into a sterile mortar, and an emulsion was made in physiologic solution of sodium chloride. Counts from the emulsion showed from 5 to 50 bacilli in a field. This emulsion was then stained in vitro by the Ziehl-Neelsen method. These emulsions were freshly prepared and injected while fresh. The animals were killed at varying intervals to see whether a prolonged period was necessary for bacillary absorption. In all of these sections, as in the previous experiments with tubercle bacilli, no bacteria were seen, nor did the tissue show evidence of tuberculous infection. In the rabbit, at least, it seemed that other factors were involved which made the absorption of the tubercle bacilli from joint cavities a different matter from the absorption of inorganic particulate matter.

Since lymphatic absorption of bacteria in massive doses had been observed from other serous cavities by a number of investigators, it was thought that repeated doses of tubercle bacilli might make possible the demonstration of the absorption of bacilli in the lymph nodes. Repeated injections might either stimulate more efficient absorption or break down any protective mechanism, if such existed, against bacillary absorption. A fresh emulsion of a relatively avirulent strain of human tubercle bacilli in physiologic solution of sodium chloride was used. Four rabbits were given injections at varying intervals.

RABBIT 1.—Ether anesthesia was used. The hair was shaved over the right knee joint. With the usual aseptic technic, 0.25 cc. of the fresh human tubercle bacilli emulsion was injected into the right knee joint. There was practically no reaction. The knee was not appreciably swollen. Two days later, and at intervals of two days, the injection of tubercle bacilli was repeated until four injections had been given. After the second injection the knee became markedly swollen, warm

55. Willis, H. S.: *Am. Rev. Tuberc.* 11:427, 1925.

and limited in motion. Swelling persisted unchanged until the animal was killed two days after the last injection. The knee contained a large amount of seropurulent fluid, which showed a number of tubercle bacilli in smears. The cartilage was a dull brownish gray; the articular capsule was thickened and injected. Smears from the common iliac lymph nodes, which were moderately enlarged, showed tubercle bacilli. Tissue was removed from the knee joint and from the common iliac nodes for microscopic study.

**RABBIT 2.**—The technic was the same as for rabbit 1; 0.3 cc. of a fresh emulsion of human tubercle bacilli was injected into the right knee joint. There was a slight swelling of the articular tissues, which lasted until the rabbit was killed. There was no observable limitation in motion. Injections were made every four days until four injections had been given. The animal was killed four days after the last injection. Smears from the joint fluid showed no bacteria. There was no definite vascular congestion of the articular capsule. The capsule of the joint was a little thickened. There was no erosion of the articular cartilage. The iliac lymph nodes were much enlarged. A smear from the right common lymph node showed tubercle bacilli. Sections of tissue were removed from the capsule of the joint and from the right common iliac lymph node for microscopic study.

**RABBIT 3.**—The technic was the same as for rabbit 1; 0.3 cc. of a fresh emulsion of human tubercle bacilli was injected into the left knee joint. There were slight swelling and slight limitation of motion in the knee, which persisted until the animal was killed. The injections of tubercle bacilli were repeated every eight days until four injections had been given. The animal was killed one week after the last injection. There was a moderate amount of seropurulent fluid in the knee joint, which showed no tubercle bacilli or smears. There were moderate hyperemia and edema of the synovial membrane. The cartilage had lost its glistening white color and was slightly eroded. The common iliac lymph nodes were enlarged, but showed no tubercle bacilli in smears taken from the incised lymph node. Sections of tissue were taken from the capsule of the joint and from the common iliac lymph nodes for microscopic study (fig. 5).

**RABBIT 4.**—The technic was the same as for rabbit 1; 0.3 cc. of a fresh emulsion of human tubercle bacilli was injected into the right knee joint. Injections were repeated every two weeks until four injections were given. The rabbit was killed ten days after the last injection. There was moderate swelling of the knee, which persisted from the first injection until the animal was killed, but there was no disturbance in function. When the knee joint was opened, a moderate increase of cloudy fluid was found. No tubercle bacilli were seen in smears. The synovial membrane was thickened; the cartilage was dull in color and showed slight superficial erosion. Sections of tissue were taken from the capsule of the joint and from the common iliac lymph node for microscopic study.

The microscopic study of the capsule and of the joints of the lymph nodes in rabbits 3 and 4 showed tuberculous inflammation. In rabbit 1, tubercle bacilli were recovered from the synovial fluid and from a swollen, common iliac lymph node (fig. 5). In rabbit 2, tubercle bacilli were found in a smear from the common iliac lymph node. The tissues from the joint and from the lymph nodes in rabbits 1 and 2 did not show definite tuberculous inflammation. Repeated injections of tubercle bacilli into the joint cavities of rabbits showed the lymphatic absorption of these bacteria to be the same as that observed for particulate matter.

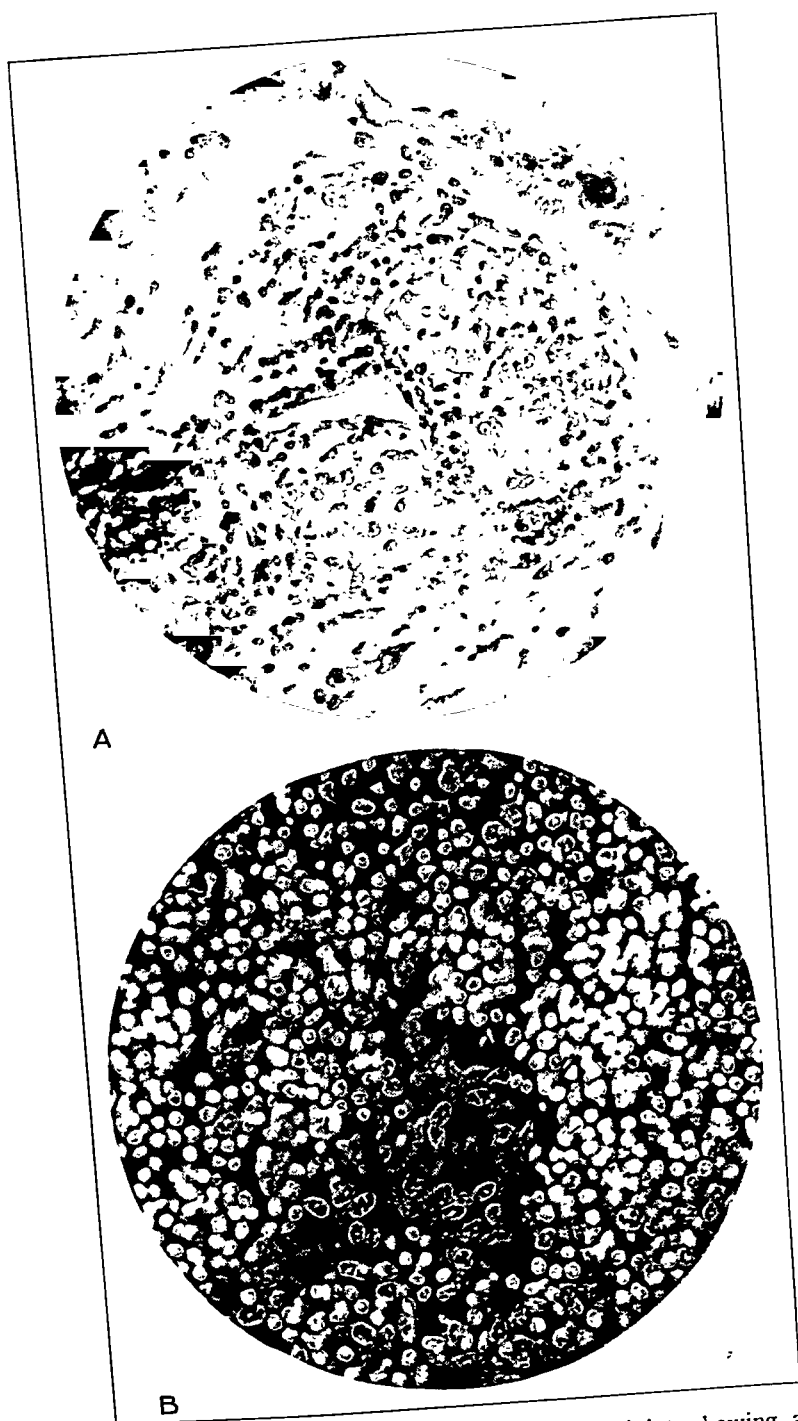


Fig. 5.—*A*, synovial membrane from the left knee joint, showing at top the serous surface of the membrane;  $\times 340$ . There are numerous epithelioid cells, but no definite tubercle formation. *B*, common iliac lymph node, with epithelioid cells and beginning tubercle formation;  $\times 425$ .

Other factors, probably chiefly chemical, played a part which made the absorption of tubercle bacilli less readily demonstrable than that of chemically inert particles. Cunningham,<sup>56</sup> Hetherington<sup>57</sup> and Wright<sup>58</sup> have described the tissue reactions which occur in tuberculous infection and after the injection of nontuberculous substances. They found that the characteristic cells of tuberculous tissue could be produced by a number of mildly irritating substances varying in chemical nature, particularly organic substances, of which macerated rabbit brain was the best. However, these authors, while noting relative differences in the time and intensity of the tissue reaction, offered no explanation for any difference in lymphatic physiology in the absorption of various organic and inorganic substances.

The mechanism involved in the removal of particulate matter from tissues and serous cavities has been the subject of controversy since the description by Beck<sup>59</sup> in 1893 of what he termed stomas in the lymphatic vessels. In 1903, MacCallum<sup>60</sup> offered evidence to show that the lymphatic system was a closed system without stomas, confirming the earlier findings of Kolosow<sup>61</sup> and Muscatello.<sup>62</sup> Bolton<sup>63</sup> and von Recklinghausen<sup>64</sup> observed the presence of particulate matter in the lymphatic vessels of the diaphragm several minutes after intraperitoneal injection, too soon, they supposed, for phagocytosis, since examination showed that the particles were free in the lymphatic vessels. Higgins and Lemon<sup>65</sup> observed powdered graphite in the diaphragmatic lymphatics four minutes after intraperitoneal injection.

Filling of the lymphatics of the capsule of the knee joint with colored solutions of dyes has been recorded by Teichmann<sup>4</sup> and by Smith and Campbell,<sup>50</sup> but in these instances the joint cavity was overexpanded before any filling of the lymphatics was observed. In such cases rupture into the lymphatics could easily have occurred. In the lymphatics of the diaphragm, Bolton<sup>63</sup> felt that the contraction of the diaphragm with alterations in intra-abdominal pressure supplied the force for the flow of fluid into the lymphatics. Drinker and Field<sup>34</sup> have noticed graphite

56. Cunningham, R. S.: *Tubercle* **12**:404, 1931.

57. Hetherington, D. C.: *Proc. Soc. Exper. Biol. & Med.* **26**:333, 1929.

58. Wright, A. W.: *Am. J. Path.* **6**:87, 1930.

59. Beck: *Wien. klin. Wchnschr.* **6**:823, 1893.

60. MacCallum, W. G.: *Anat. Anz.* **23**:157, 1903; *Arch. f. Anat. u. Entwicklungsgesch.*, 1902, p. 273.

61. Kolosow, A.: *Arch. f. mikr. Anat.* **42**:318, 1893.

62. Muscatello, G.: *Virchows Arch. f. path. Anat.* **142**:327, 1895.

63. Bolton, C.: *J. Path. & Bact.* **24**:429, 1921.

64. von Recklinghausen: *Die Lymphgefäße und ihre Beziehung zum Bindegewebe*, Berlin, A. Hirschwald, 1862; *Virchows Arch. f. path. Anat.* **24**:172, 1863.

65. Higgins, G. W., and Lemon, W. S.: *Am. J. M. Sc.* **178**:536, 1929.

particles in the subcutaneous lymphatics five minutes after their injection into the subcutaneous tissues when the animal was active. They concluded that motion or massage caused the lymphatic vessels to lose their anatomic integrity and to become momentarily open into the tissue spaces. Practically all modern study has tended to disprove the presence of stomas or constant openings of any sort into lymphatic vessels. In microscopic sections from rabbits' joints, particles were often seen in the interstices and beneath the lining synovial cells, apparently free in the tissues. The work of Ryneerson<sup>66</sup> and Cunningham<sup>67</sup> on this problem has suggested a fairly loose union of the lining cells, so that mechanically small particles might pass between the lining cells and readily lodge in the tissues beneath.

The cells that play the chief rôle in phagocytosis of particles in serous cavities are the endothelial cells of the reticulo-endothelial system. Their origin has not been definitely established (Cunningham<sup>67</sup>). Their presence in normal, circulating lymph has been denied (Kindwall<sup>68</sup>). Gay,<sup>69</sup> who has studied the problem of the origin of these phagocytic cells in relation to tissue resistance, believed that these phagocytic cells of serous cavities, the histiocytes, come from the clasmato-cytes of connective tissue. Phagocytosis by such cells is the chief method, probably the only method, with present histologic and physiologic understanding, by which particles larger than molecular size enter the lymphatics. Clark<sup>70</sup> has described the phagocytosis of fat droplets in the tails of tadpoles by cells which then entered the lymphatic vessels. The wide potential spaces between the cells of the lymphatic vessel wall and the arrangement of the cells like tiles on a roof have been suggested by Muscatello<sup>62</sup> as a provision for the easy entrance of phagocytic cells into the lymphatic vessels.

Material larger than molecular size is taken up from the tissues by blood vessels only under unusual conditions, if at all. Krogh<sup>71</sup> has mentioned the possibility of such absorption where the blood vessels are extremely dilated, but no observation of such occurrence is on record. W. J. Mayo<sup>72</sup> stated that except in the gastro-intestinal tract the blood vessels are impervious to particulate matter and colloidal substances.

66. Ryneerson, E. H.: *J. Bone & Joint Surg.* **13**:127, 1931.

67. Cunningham, R. S.: *Physiol. Rev.* **6**:242, 1926.

68. Kindwall, J. A.: *Bull. Johns Hopkins Hosp.* **40**:39, 1927.

69. Gay, F. P.: *Tissue Resistance and Immunity*, *J. A. M. A.* **97**:1193 (Oct. 24) 1931.

70. Clark, E. R.: *Am. J. Anat.* **21**:421, 1916.

71. Krogh, August: *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1922.

72. Mayo, W. J.: *The Significance of Lymphatic Involvement in Infections*, *J. A. M. A.* **80**:221 (Jan. 27) 1923.

Katsura,<sup>73</sup> working on the absorption of dyes from the pleural and peritoneal cavities of dogs and rabbits, found that crystalloid stains are absorbed rapidly through the blood stream, while colloidal stains are absorbed more slowly through the lymphatics. In rabbits, I observed complete absorption of soluble dyes, such as methylene blue (methylthionine chloride, U. S. P.) or carmine, twenty-four hours after their injection into joint cavities. There was usually staining of the entire joint capsule, but no trace of soluble dye could be seen in the lymph nodes draining that joint cavity. Nonsoluble dyes, particulate matter or colloidal, such as india ink, were absorbed much more slowly, some dye remaining ensheathed in fibrin or fibrous tissue within the articular cavity often for months after its injection. During the time, in animals killed at lengthening intervals, a gradually increasing accumulation of the dye was seen in the lymph nodes draining those tissues. £

Herring and MacNaughton,<sup>54</sup> in making investigations on the absorption of particulate matter from the lungs, concluded that both india ink and the tubercle bacillus were taken up in the same manner by phagocytes and carried to the lymphatics in the human lung. This was also found to be true in the joint cavity of rabbits, although bacteria were not demonstrable with the same regularity as particulate matter. In studying the removal of colloidal and particulate carbon from the knee joint in rabbits, Key<sup>35</sup> concluded that most of the injected material was carried by macrophages to lymphatic capillaries. When the macrophages died, the particulate matter that they were transporting was picked up and carried by succeeding generations of phagocytes. The particles were found first in lymph nodes and later in the liver, spleen and bone marrow. Ryneerson<sup>66</sup> found that particles from joint cavities lodged in all tissues of the reticulo-endothelium system.

Job<sup>53</sup> and Herring and MacNaughton<sup>54</sup> found that the lymph sinuses of the first proximal lymph node draining the area studied acted as efficient filters for the material brought to them by the phagocytic cells. They believed that material was carried only to more proximal lymph nodes, through the lymphatic anastomoses around the lymph node, when it came in too large quantities to be taken care of adequately by the first lymph node reached. No lymphatics have been found unconnected with lymph nodes. In my study of the drainage of the joints of the lower extremity, no india ink was ever seen in lymph nodes above those along the lumbar spine, nor was any found in the anterior mediastinal lymph nodes. The work of Poynter<sup>74</sup> gave a possible explanation for this. From his experiments he concluded that the lymphatic drainage from the lower extremity passed through the anterior mediasti-

73. Katsura, S.: *Tohoku J. Exper. Med.* **5**:263, 1924.

74. Poynter, C. W. M.: *Colorado Med.* **23**:386, 1926.

nal lymphatics and not through the thoracic duct. He found that the thoracic duct drained only the peritoneal and pleural cavities.

In the beginning of this study, dyes mixed with irritating substances, such as ether and turpentine, as advocated by Gerota,<sup>75</sup> were injected into the joints of living animals. The studies had to be given up, because there was very little absorption from the articular cavities, with practically no deposition of the dye in the lymph nodes. At the same time a violent inflammation was produced in the joint, which subsided in one or two weeks. This led to the conclusion that the inflammation had in some way hindered the mechanism of absorption through the lymphatics. Notkin<sup>76</sup> was able to impede absorption from the peritoneal cavity in dogs by the intraperitoneal injection of irritating substances. He determined the average time required for the appearance of hemoglobin or india ink in the lymph of the thoracic duct after intraperitoneal injection into normal dogs. After he had produced a peritoneal inflammation by the intraperitoneal injection of a solution of potassium iodide, he found that the time required for the first appearance of the hemoglobin or india ink after intraperitoneal injection was about three times as great as in normal dogs. Microscopic studies of the central tendon of the diaphragm, after injections of potassium iodide, showed most of the lymphatics shrunken and many of them obliterated, where normally a rich plexus of lymphatic vessels was found.

These observations led to further study of lymphatic absorption from joint cavities after the production of a synovitis. After the trial of a large number of substances, a 20 per cent solution of potassium iodide was found to be most satisfactory. The local pharmacologic action of this drug has recently been described by Cameron.<sup>76</sup> In single injections into joint cavities, it produced a mild inflammation, but rarely any serious damage to any articular structures. Injections of 0.5 cc. were made into the knee joints of rabbits; 0.25 cc. was injected when the elbow joint was used. Such injections produced an inflammatory exudate within the joint cavity within from six to twelve hours after injection. The knee or elbow became moderately swollen, but there was no appreciable increase in surface temperature, and there was no apparent limitation in active or passive motion in the joint into which the injection was made. The swelling of the joint lasted usually from two to five days and then subsided. Repeated injections produced the same effect, with a little slower subsidence of subsequent exudations. Within two or three weeks a definite thickening of the joint capsule could be felt in most of the animals. Smears of the joint exudate showed polymorphonuclear cells, lymphocytes and a rather small number

75. Notkin, J. A.: *Virchows Arch. f. path. Anat.* **225**:47, 1925.

76. Cameron, D. F.: *A Comparative Study of Sodium Iodid as an Opaque Medium in Pyelography*, *Arch. Surg.* **1**:184 (July) 1920.



of large mononuclear cells, some containing injected polymorphonuclear cells (Higgins and Lemon<sup>45</sup>).

In five rabbits a single injection of a 20 per cent solution of potassium iodide was made into the knee joint. The animals were killed at varying intervals to determine the extent and duration of tissue changes as well as the effect on the local lymphatics and their absorptive function. The synovial lymphatics were studied by several methods. Thin sheets of synovial membrane were treated with hydrogen dioxide. By this method lymphatics in the depths of the tissue were never demonstrated, nor were the lymphatics shown well in fixed sections. Injections of particulate matter gave data of a decreased function. Injections of india ink given a day or longer before the animal was killed gave suggestive information of the rate of lymphatic absorption. Injections of a 0.5 to 1 per cent solution of mild silver protein into the joint cavity several hours before the animal was killed gave an even more satisfactory demonstration of the lymphatics than was obtained with hydrogen dioxide, with the added advantage that it could be shown better in fixed sections.

**RABBIT 1.**—Ether anesthesia was used. The hair was shaved over the right knee joint. The skin was painted with alcohol and with 3 per cent iodine. With a 25 gage needle, 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the knee joint. The joint was moderately swollen the following day. The swelling subsided in two days. The animal was killed after three days. There was a moderate increase of turbid fluid in the knee joint. The cartilage was dull, instead of the usual glistening white. The synovial membrane appeared normal. Sections were taken from the synovial membrane of both knee joints for study immediately with hydrogen dioxide. Tissue was also removed from both knee joints for microscopic study.

**RABBIT 2.**—The technic was the same as for rabbit 1; 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the right knee joint. There was moderate swelling of the knee joint, which subsided in four days. The animal was killed five days after receiving the injection. The cartilage was dull instead of the usual glistening white. There was no increase of fluid in the joint cavity. The synovial membrane appeared normal. Sections were taken from the synovial membrane of both knees for microscopic study. Small pieces of the synovial membrane of both knees were treated with hydrogen dioxide and studied immediately for lymphatics.

**RABBIT 3.**—The technic was the same as for rabbit 1; 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the left knee joint. There was slight swelling of the joint, which subsided in two days. The animal was killed in one week. No increased amount of fluid was seen in the knee joint. The cartilage and synovial membrane appeared normal. Sections were taken from the synovial membrane for study. Sections from the synovial membrane of both knees were treated immediately with hydrogen dioxide and examined under the microscope for lymphatic vessels.

**RABBIT 4.**—The technic was the same as for rabbit 1; 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the right knee joint. There was slight swelling of the joint, which subsided in three days. Four days after

injection, 0.4 cc. of a 0.5 per cent solution of mild silver protein (argento-proteinum mite, U. S. P.) was injected into both knees. Four hours after the injection of the silver protein, the animal was killed. Sections of the synovial membrane of the two knees were taken for later microscopic study, and other sections were studied immediately with transmitted light under the microscope.

RABBIT 5.—The technic was the same as for rabbit 1; 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the left knee joint. There was slight swelling of the left knee, which subsided in three days. Six days after injection 0.4 cc. of a 0.5 per cent solution of mild silver protein was injected into the joints of both knees. The rabbit was killed five hours later. Sections were taken from the synovial membrane of both knees, and the lymphatics were studied immediately. Other sections were taken for fixed microscopic preparations.

It was hoped that by the injection of a solution of potassium iodide a mild inflammatory process would be initiated and eventually a mild arthritis produced. Such attempts had been made by Key<sup>77</sup> and Rynearson<sup>66</sup> with various substances. After injections of potassium iodide, there was an exudation of fluid into the joint, and there were slight proliferation of the synovial membrane and dilatation of the blood vessels (fig. 6). The pathologic picture was similar to that described by Key<sup>77</sup> in early experimental arthritis. In all animals that were permitted to live longer than one week, the synovial membrane appeared normal. Examination of the lymphatics with hydrogen dioxide in rabbit 1 showed a decrease in the number of lymphatic vessels in comparison with the number seen in normal synovial membrane. At the same time, the lymphatic vessels that were present were larger than those seen in synovial tissue from the normal joint. A similar but less marked condition was observed in the lymphatics of rabbit 2. In rabbit 3, no difference could be made out between the lymphatics on the two sides. This was probably due to the fact that the joint had wholly recovered from the mild inflammatory reaction produced by the solution of potassium iodide. In rabbits 4 and 5, into the knee joints of which a diluted suspension of colloidal silver was injected a few hours before the animal was killed, the lymphatic vessels were stained a yellowish brown from the absorption of the colloidal silver, and they could be demonstrated more readily than when hydrogen dioxide was used. In rabbit 4, the lymphatic vessels were larger but less in number than those seen in the knee not receiving an injection. In rabbit 5, no difference could be seen between the lymphatics from the synovial membrane of the right and the left knee joints. The inflammatory reaction had subsided, and the lymphatics had apparently recovered from any injury they had suffered.

Since the inflammatory reaction in the knee joint after one injection of potassium iodide was of such a short duration, several injections of

77. Key, J. A.: *J. Bone & Joint Surg.* 11:705, 1929.

potassium iodide were given at weekly intervals in an attempt to produce a more lasting change in the lymphatics. Five rabbits were given two injections of potassium iodide at weekly intervals.

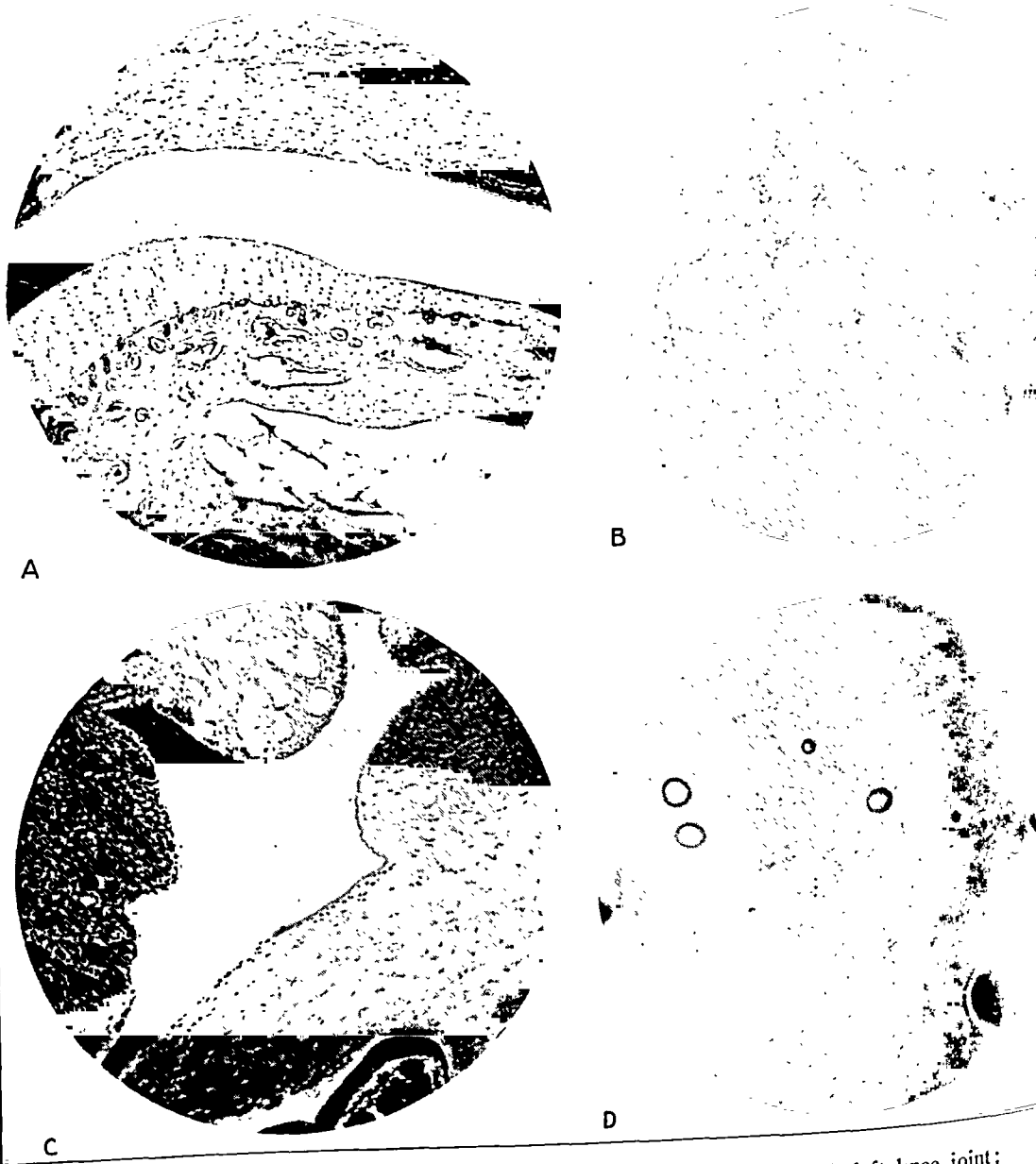


Fig. 6 (rabbit 1).—*A*, synovial membrane of the (uninjected) left knee joint; reduced from  $\times 70$ . *B*, same as *A*, treated with hydrogen dioxide, showing the superficial lymphatic vessels; reduced from  $\times 80$ . *C*, synovial membrane of (injected) right knee joint, showing slight vascular congestion, edema and endothelial proliferation; reduced from  $\times 90$ . *D*, same as *C*, treated with hydrogen dioxide. There are fewer and shorter lymphatic vessels; reduced from  $\times 80$ .

RABBIT 1.—With the usual aseptic technic, 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the right knee joint. There was moderate swelling of the knee, which subsided in three days. Seven days after the first injection, a second injection of 0.5 cc. of a 20 per cent solution of potassium iodide was made into the same joint.

Following this injection, a moderate swelling appeared which persisted until the animal was killed five days after the last injection. There was a little thickening of the synovial membrane, with projecting, thickened, villus-like processes. The synovial membrane was a deeper red than that on the side on which no injection was made. The cartilage was dull gray and not glistening. Sections from the synovial membrane were treated with hydrogen dioxide and studied under the microscope. On the side into which an injection was made, only an occasional short lymphatic vessel was seen, while a fairly numerous distribution of lymphatics was observed in the synovial membrane on the side not receiving an injection. Sections were taken from both knees for microscopic study.

RABBIT 2.—The same technic was used as for rabbit 1; 0.5 cc. of a 20 per cent solution of potassium iodide was injected into the right knee joint. There was slight swelling of the joint, but no disturbance of function. Swelling disappeared in two days. Six days later a second injection was given. The knee remained swollen for five days. The animal was killed on the seventh day after the last injection. There was no increase of fluid in the knee joint. The synovial membrane showed moderate vascular congestion. The synovial membrane from the knee that had received injections was also thicker. The cartilage was not eroded, but had lost its glistening white appearance. Small sections from the synovial membrane of both knees were treated immediately with hydrogen dioxide. On the side receiving the injection only, one short but rather thick lymphatic vessel was found. A moderate number of small lymphatic vessels were seen in tissue from the side into which no injection was made. Sections were taken from both knees for microscopic study.

RABBIT 3.—The technic was the same as for rabbit 1, except that the joints of the foreleg (humero-ulnar), as well as the joints of the knee, were used. Five-tenths cubic centimeter of a 20 per cent solution of potassium iodide was injected into the right knee joint, and 0.25 cc. into the joint of the right foreleg. There was a slight swelling which disappeared in both joints by the third day. A second injection of like amount was made into both the knee joint and the foreleg joint on the seventh day. The swelling persisted in the foreleg joint for five days, and had not disappeared from the knee joint when the animal was killed on the fourteenth day after the last injection. Four hours before the animal was killed, 0.4 cc. of a 1 per cent solution of mild silver protein was injected into both knee joints, and 0.2 cc. was injected into the joints of both forelegs. At autopsy, there was a little increase in the fluid in all four joints. The synovial membrane was thicker in the right knee joint and right foreleg joint and showed moderate vascular congestion. The cartilage was not eroded, but appeared dull gray on the right side, and white and glistening on the left side. The sections of tissue from the synovial membrane were studied immediately under the microscope with transmitted light. On the right side, the sections from the knee and foreleg were similar. They showed only an occasional large lymphatic vessel. On the left side, a fairly extensive plexus of small lymphatic vessels was observed in tissue from the joints of both the knees and the forelegs. Sections were taken from the four joints for further study.

**RABBIT 4.**—The procedure was the same as for rabbit 3. After the first injection of potassium iodide, there was slight swelling in both joints receiving injection, which persisted to the second injection on the sixth day. Following the second injection, there was moderate swelling, but no appreciable limitation in motion, which lasted until the animal was killed on the fourteenth day after the first injection. One day before the animal was killed, 0.4 cc. of india ink, diluted with equal parts of distilled water, was injected into both knee joints. Three hours before the animal was killed, 0.2 cc. of 1 per cent solution of mild silver protein was injected into the joints of both forelegs. When the joints of both knees were opened, it was seen that the joint cavity of the right knee appeared to contain much more ink than that of the left knee. The synovial membrane was thicker and seemed to be more congested on the right side. Sections were taken from the joints of both forelegs and studied immediately with the microscope. On the right side, only a few short lymphatics were seen; on the left, there was an extensive plexus of lymphatic vessels. Sections were taken from the four joints and the regional lymph nodes for microscopic study.

**RABBIT 5.**—The same procedures were carried out as for rabbit 3. After the first injection into the right side, there was moderate swelling in both joints, which lasted three days. On the seventh day, the injection was repeated. The swelling subsided in five days in the joint of the right foreleg and in six days in the joint of the right knee. The animal was killed eighteen days after the beginning of the experiment. One day before the animal was killed, 0.4 cc. of india ink, diluted with equal parts of distilled water, was injected into both knee joints and 0.2 cc. into both foreleg joints. The synovial membrane in the right knee and the right foreleg was a little thicker and seemed to have more india ink on its surface than the synovial membrane from the joints on the left side. Sections were taken from both knee joints and both foreleg joints for immediate study of the lymphatics with hydrogen dioxide. No appreciable difference could be determined between the lymphatics on the side into which an injection was made and the other side. Tissue was also removed from both knee and both elbow joints for histologic study.

In another series of five rabbits, three weekly injections of potassium iodide were given. The same procedures were carried out as described in the last series. Since the findings were similar in all, only the noteworthy features in each animal will be mentioned. The microscopic observations in both series will be described together.

**RABBIT 1.**—The procedure was the same as in the last series of rabbits. After the first injection, there was swelling which persisted in both the right foreleg and the right knee joints until the animal was killed one week after the last injection. There was a moderate increase in cloudy fluid in both of the joints into which injections had been made. The synovial membrane was thickened and edematous and was moderately engorged with blood. The cartilages were a dull brownish gray, but no erosion was evident. Sections from the knee and foreleg were studied immediately with hydrogen dioxide. No lymphatics could be demonstrated in the synovial tissue from the right knee and right elbow, while a moderate number of lymphatics could be seen in tissues of the synovial membrane from the left knee and left foreleg joints. Tissues from both knee joints and both foreleg joints were removed for later microscopic study.

**RABBIT 2.**—In this rabbit swelling of the right knee joint and right foreleg joint lasted three days after the first injection, and, after the second injection,

remained practically unchanged until the animal was killed one week after the last injection. There was no demonstrable disturbance in function. When the right knee and foreleg joints were opened, there was a moderate amount of thin, turbid fluid. The synovial membrane showed venous congestion and was moderately thickened. There were a number of thickened villus-like projections about the margins. The cartilage showed no erosion, but was a dull grayish brown. Sections of the synovial membrane treated with hydrogen dioxide showed an occasional short lymphatic vessel on the right, while there was a fairly abundant plexus of small lymphatic vessels on the left. Sections were taken from the four joints for microscopic section.

**RABBIT 3.**—After the first injection into the right knee and elbow joints, there was a moderate amount of swelling in both of the joints, with limitation of motion in the right knee, which lasted until the animal was killed six days after the last injection. Into both knee joints and both foreleg joints a 1 per cent solution of mild silver protein was injected four hours before the animal was killed. Sections of the synovial membrane studied immediately showed few lymphatic vessels on the right, while numerous lymphatic vessels were seen in the synovial tissue on the left side. Synovial membrane from both knee joints and both foreleg joints was removed for histologic study.

**RABBIT 4.**—There was moderate swelling after the first injection, which lasted four days. Swelling persisted after the second injection into the right knee and elbow joints on both sides, with a little disturbance in function in the knee joint and elbow joint until the animals were killed six days after the last injection. A 1 per cent solution of mild silver protein was injected into both knee joints and both elbow joints four hours before the animal was killed. The joints on the right showed findings similar to those already described in the series. Sections from the synovial membranes studied immediately showed only an occasional short segment of a lymphatic vessel on the right, while there were numerous small lymphatics in the synovial tissue taken from the left knee and elbow joints.

In this animal, there were rather marked and persistent swelling and a little limitation of motion in both the knee joint and the elbow joint from the first injection until the animal was killed six days after the last injection. Two days before the animal was killed, 0.4 cc. of india ink was injected into both knee joints, and 0.2 cc. of india ink was injected into both elbow joints. When the joints were opened, there was apparently moderate absorption of the india ink on the left side, while there was no evidence of absorption of the india ink on the right side, and there was no visible deposition of the india ink in the regional lymph nodes on the right side, while the regional lymph nodes on the left side were deeply stained. Tissues were taken for microscopic study.

The microscopic sections from these two series were similar (fig. 7). The joints that had received three injections of potassium iodide as a rule showed more inflammatory changes than the joints that had received two injections. There was increased proliferation of the synovial membrane with occasional lymphocytic infiltration about the blood vessels. There was a little increase in the number of fibroblasts and in the fibrous tissue in the subserous layer of the synovial membrane, with lymphocytic infiltration occasionally about the blood vessels. The cartilage in a few sections showed necrosis of the superficial cartilage cells, with slight erosion of the surface, but, as a rule, there were

no changes observable in the cartilage. The bone and marrow cavity showed nothing unusual. It was possible only occasionally to demonstrate the silver protein or india ink in the lymphatics in microscopic

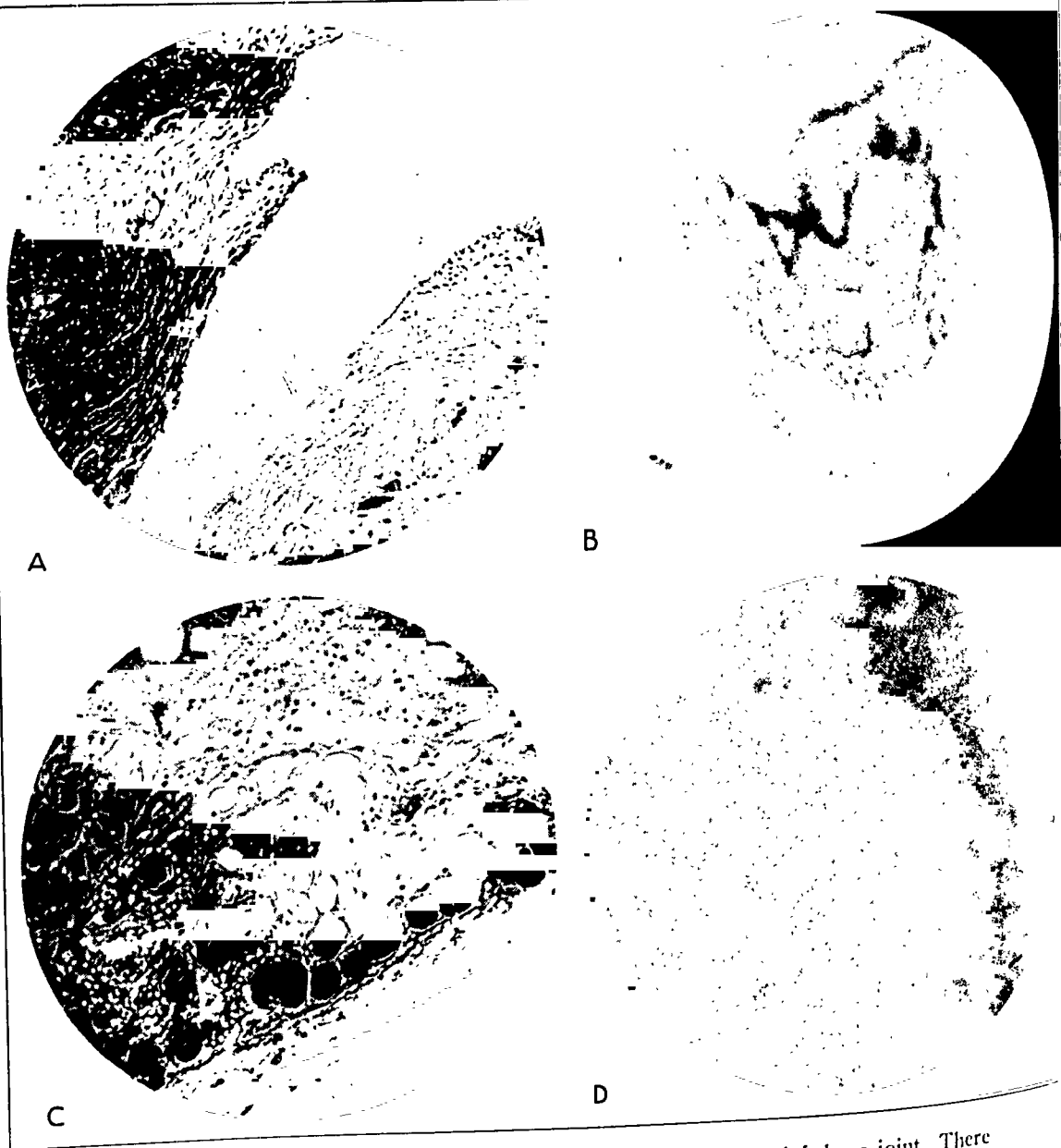


Fig. 7 (rabbit 3).—*A*, synovial membrane of (uninjected) left knee joint. There is very little silver in or on the synovial membrane; reduced from  $\times 80$ . *B*, same as *A* (fresh tissue). The lymphatic vessels are filled with silver-containing phagocytes; reduced from  $\times 80$ . *C*, synovial membrane of (injected) right knee joint, showing silver particles chiefly on the synovial surface, edema of tissues, vascular engorgement and endothelial proliferation; reduced from  $\times 90$ . *D*, same as *C* (fresh tissue); a few silver-stained lymphatics are visible.

sections, although the lymphatic vessels filled with silver protein could be traced fairly easily in fresh tissue. In a few, where they were cut across transversely, they could be definitely identified, and the sections were in practically all cases from the synovial membrane of joints not receiving injections. In the tissues from the joints into which injections of potassium iodide, india ink and, to a less extent, the silver protein were made, the substance was seen either in phagocytic cells or enmeshed in fibrin, for the most part on the surface of the synovial membrane.

The investigations of Ryneerson<sup>66</sup> and Key<sup>37</sup> suggested that practically all particulate matter was carried by macrophages to the lymphatic vessels. While particles might be forced mechanically between a rather loose syncytium of synovial cells, penetration of particles to any appreciable depth into the synovial tissue was impossible without the action of phagocytic cells. The recent work of Sigurdson<sup>78</sup> has shown that no openings or stomas were demonstrable on the surface of the synovial membrane. Where absorption of particulate matter did not occur in the experiments recorded in this paper, there were two possible causes. The material was not picked up by macrophages, or the lymphatics were changed, so that the entrance of phagocytes was prevented. Absence or nonactivity of phagocytic cells has been observed in a number of diseases, but discussion of these is beyond the scope of this paper. In the microscopic sections phagocytic cells filled with particulate matter were observed in large numbers on the serous surface of the synovial membrane, which suggested that they were unable to go deeper into the tissues, because they could not enter lymphatic channels as in normal tissue.

In order to find out how long these changes in the joints persist, another series of four rabbits was given three injections of potassium iodide at weekly intervals. These rabbits were killed one, two, three and four months, respectively, after the last injection.

**RABBIT 1.**—The technic was the same as in the previous series. The swelling disappeared in the joints into which injections were made (right knee and right foreleg) ten days after the last injection. Two-tenths cubic centimeter of mild silver protein solution was injected into the right foreleg and 0.4 cc. into the right knee joint five hours before the animal was killed. The same injections were given in the opposite (normal) elbow and knee joints. When the animal was killed one month later, there was still moderate thickening of the joint capsule. Sections studied immediately with the microscope showed only an occasional lymphatic vessel in the synovial tissues from the joints into which injections were made, while an extensive lymphatic plexus was shown in the synovial tissue from the other side.

Microscopic study showed a moderate proliferation of the synovial membrane, with increased fibrous tissue in the subserous layer on the right side. There was

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78. Sigurdson, L. A.: *J. Bone & Joint Surg.* **12**:605, 1930.



occasional lymphatic infiltration about the blood vessels. There were no definite changes in the bone, cartilage or marrow cavity.

**RABBIT 2.**—In this rabbit there was swelling of the injected joints, the left knee and foreleg joints, into which injections were made, until one week after the last injection. There was practically no disturbance of function in these joints. There was still moderate capsular thickening about the joints when the animal was killed two months after the last injection. A 1 per cent solution of mild silver protein was injected into both knee and both foreleg joints four hours before the animal was killed. Sections from the synovial membrane studied immediately showed a slightly more abundant plexus in the synovial membrane from the joints on the right side than from that on the left side. There was slightly greater synovial proliferation on the left side, but there were no striking pathologic changes in the joints which had received the injections of potassium iodide.

**RABBIT 3.**—Swelling was present in the joints into which injections were made, from the first injection until two weeks after the third injection. Definite capsular thickening could be made out about the injected knee joint until the animal was killed three months after the last injection. Four-tenths cubic centimeter of a 1 per cent solution of mild silver protein was injected into both knee joints, and 0.2 cc. into the joints of both forelegs five hours before the animal was killed. There were no apparent macroscopic pathologic changes in any of the joints. Tissue from the synovial membrane studied immediately showed no noteworthy difference in the number and size of the lymphatic vessels from the two sides. The microscopic sections showed no pathologic changes.

**RABBIT 4.**—Swelling subsided five days after the first injection, but remained practically unchanged in the joints after the second injection until ten days after the last injection. There was appreciable capsular thickening about the knee joint into which an injection was made for about two months. The animal was killed in four months. Mild silver protein was injected into both knee and both foreleg joints four hours before the animal was killed. Tissue studied immediately showed an equally dense lymphatic plexus on both sides. There were no definite pathologic changes in the tissues from the joints that had been given injections of potassium iodide.

These experiments showed that the changes produced in the joints by injections of potassium iodide were in no wise permanent, but gradually subsided in about two months, varying somewhat in different animals. Similar results were obtained by Key,<sup>77</sup> who observed a partial return to normal conditions within twelve days after single injections of india ink or citrated blood into joint cavities. His work suggested that the duration of the inflammation of the synovial tissue might depend somewhat on the severity of the reaction produced, and, also, on the number of injections given. A series of seven animals was given from seven to twelve injections of potassium iodide at weekly intervals to see how long changes in the joints could be made to persist. In the last four animals emulsions of tubercle bacilli were injected into the knee joint for several weeks at weekly intervals before the animals were killed. No infections in the joints into which injections were made were seen, and cultures from the joints were negative at autopsy.

RABBIT 1.—The technic was the same as in previous series. Seven injections of a 20 per cent solution of potassium iodide were made at weekly intervals into the joint cavities of the right knee and foreleg. Swelling subsided in the joints two weeks after the last injection. There was still some palpable thickening of the capsule of the right knee joint when the animal was killed four months after the last injection. A 1 per cent solution of mild silver protein was injected into both knee and both elbow joints five hours before the animal was killed. Both the right knee and the right foreleg showed moderate thickening of the synovial membrane. The cartilage was dull, but otherwise showed no macroscopic pathologic change. Tissue from the synovial membrane studied immediately showed only a few lymphatic vessels on the right side and a fairly numerous plexus on the left side. Microscopic section showed moderate epithelial proliferation of the lining cells. There was a moderate increase in the fibrous tissue in the subserous layers. There was slight lymphocyte infiltration in the synovial membrane, particularly about the blood vessels. The cartilage showed no pannus. There were a few areas of superficial erosion. No changes were seen in the bone or marrow cavity.

RABBIT 2.—In this rabbit nine injections of a 20 per cent solution of potassium iodide were given at weekly intervals. Swelling persisted in the joint for two weeks after the last injection. There was periarticular thickening which remained practically unchanged until the animal was killed six months later. A 1 per cent solution of mild silver protein was injected into both knee and elbow joints four hours before the animal was killed.

Sections of the joint studied immediately showed no lymphatics on the right side and a fairly numerous plexus on the left side. The synovial membrane was moderately thickened. The cartilage showed no change. Fixed sections of tissue showed proliferation of the synovial endothelial cells with a little increase in the fibrous tissue beneath. There was no change in the bone or bone marrow.

RABBIT 3.—This rabbit was given ten injections of potassium iodide at weekly intervals into the right knee and right foreleg joints. The swelling persisted for eighteen days after the last injection. The animal was killed five months after the last injection. Four hours before the animal was killed, a 1 per cent solution of mild silver protein was injected into both knee and both foreleg joints. Synovial membrane studied immediately showed only one short lymphatic vessel on the right side and a moderate number of lymphatic vessels on the left side. Fixed sections showed a moderate endothelial proliferation of the synovial membrane with fibrous proliferation in the subserous layer of the synovial membrane and occasional lymphocytic infiltration about the blood vessels. The cartilage, bone and bone marrow showed no pathologic changes (fig. 8).

RABBIT 4.—This animal was given ten injections of potassium iodide at weekly intervals into the right knee joint and right foreleg joint. Swelling of the joints into which injections were made lasted for three weeks after the last injection. Periarticular thickening could be felt about the right knee until the animal was killed seven months later. During the last month that the animal remained alive, 0.3 cc. of a suspension of human tubercle bacilli of low virulence was injected at weekly intervals for three times into the right knee joint. A 1 per cent solution of mild silver protein was injected into both foreleg joints five hours before the animal was killed. Smears from the right knee showed tubercle bacilli. The synovial membrane was moderately thickened. There were discoloration and slight roughening of the articular cartilage. Sections from the synovial membrane studied immediately with the microscope demonstrated no lymphatics stained by

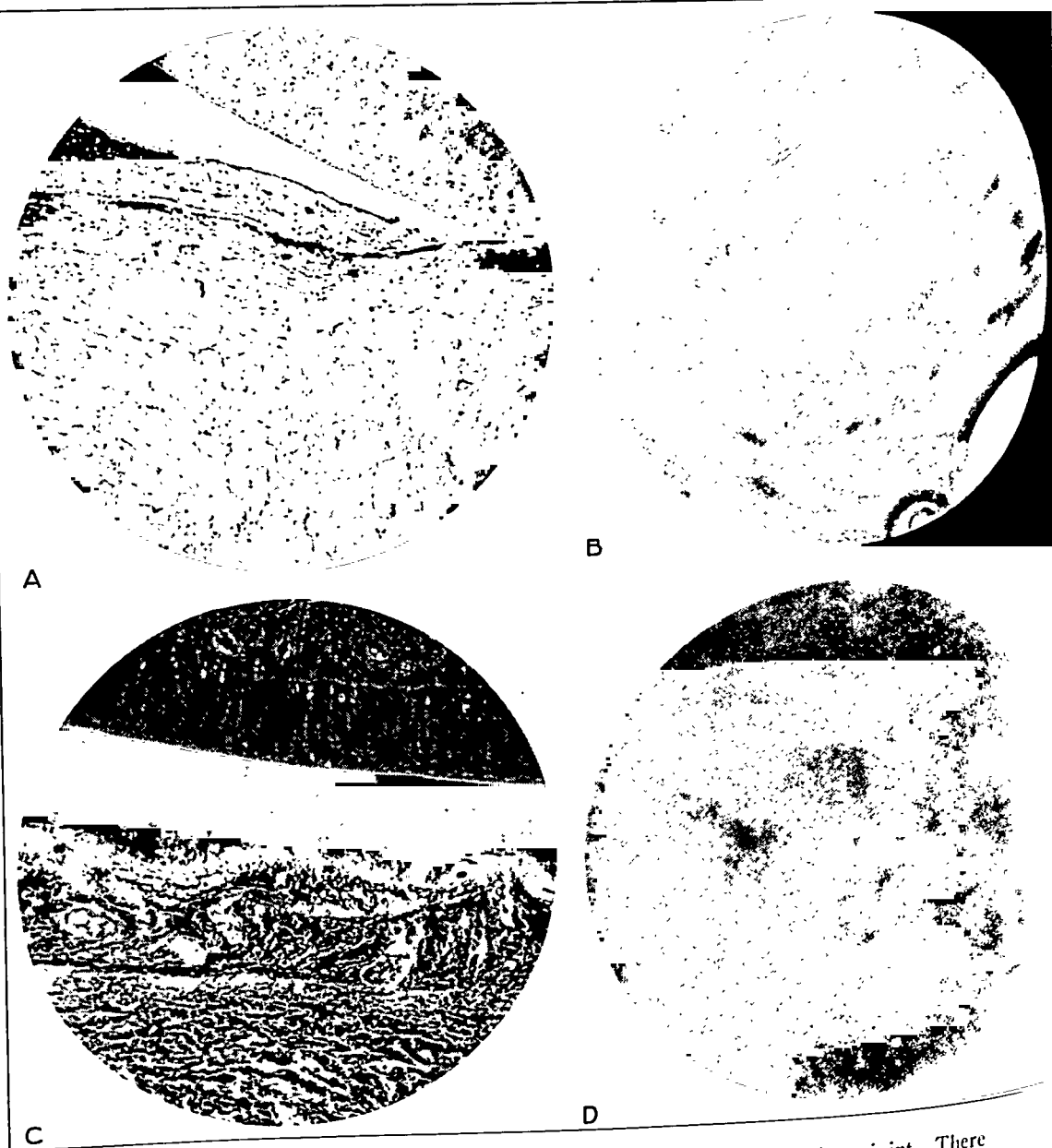


Fig. 8 (rabbit 3).—*A*, synovial membrane of (uninjected) left knee joint. There is a little silver on the synovial surface and in the tissues; reduced from  $\times 80$ . *B*, same as *A* (fresh tissue). The lymphatics filled with phagocytes, which have taken up silver particles, are fairly numerous; reduced from  $\times 80$ . *C*, synovial membrane of (injected) right knee joint; reduced from  $\times 100$ . Note the large amount of silver on the synovial membrane. There are extensive synovial proliferation, vascular congestion and fibrosis. *D*, same as *C*; reduced from  $\times 80$ . The silver on the synovial surface gives the dark appearance. No lymphatics are visible.

the silver protein on the right side, but showed a fairly numerous plexus of lymphatic vessels on the left side. Microscopic sections showed endothelial proliferation of the synovial membrane, with dilatation of the superficial blood vessels. There was a moderate increase in the subserous fibrous tissue. There was no lymphocytic perivascular infiltration. No evidence of tuberculosis was seen in the synovial membrane, nor were tubercle bacilli seen in sections stained to demonstrate them. The regional lymph nodes showed no evidence of tuberculous infection.

RABBIT 5.—This rabbit was given ten injections of potassium iodide at weekly intervals into the right knee and foreleg joints. Swelling of the knee joints lasted for almost four weeks after the last injection. There was periarticular capsular thickening, which persisted until the animal was killed eight months later. In spite of this, there was no appreciable disturbance in function after the swelling of the knee joints had subsided. A suspension of human tubercle bacilli of low virulence was injected at weekly intervals for three times into the right knee joint, which had previously received injections of potassium iodide. The animal was killed one week after the last injection of tubercle bacilli. A 1 per cent solution of mild silver protein was injected into both elbow joints four hours before the animal was killed. There was definite and rather marked thickening of the synovial membrane in the right knee and elbow joints. The cartilage was dull in appearance and was slightly roughened. Smears from the joint cavity showed tubercle bacilli. The regional lymph nodes were not enlarged. Sections from the synovial membrane studied immediately showed no lymphatic vessels on the right side and a fairly abundant plexus of lymphatics in the synovial membrane on the left side. Fixed sections from the right knee joint showed marked thickening of the joint capsule with increased villous formation. There was extensive proliferation of the synovial endothelium. There was occasional lymphocytic infiltration about the blood vessels and in the subserous tissue. There were moderate edema and vascular congestion of the synovial membrane. Slight fibrosis was noted in the subserous synovial tissue. There were many more lymph vessels containing phagocytes, with silver particles in the tissue from the left side, which showed no pathologic changes. The cartilage of the right knee showed slight superficial erosion. The bone marrow cavity showed no abnormality. The regional lymph nodes showed no tubercle bacilli and no evidence of tuberculous infection.

RABBIT 6.—This rabbit was given twelve injections of potassium iodide at weekly intervals into the right knee and foreleg joints. Swelling of the joints lasted for four weeks after the last injection. Palpable capsular thickening could be felt about the joints into which injections were made until the animal was killed ten months after the last injection. One month before the animal was killed and at weekly intervals thereafter for two subsequent times, a suspension of avirulent human tubercle bacilli was injected into the right knee joint. Four hours before the animal was killed, a solution of mild silver protein was injected into both elbow joints. When the joints were opened, a marked thickening of the joint capsule with villous formation was observed on the right side. There was slight erosion of the cartilage, which had a dull brownish color. Smears from the joint cavity of the right knee showed a few tubercle bacilli. The regional lymph nodes were not enlarged. Tissue from the synovial membrane of the right foreleg showed no lymphatics, while an extensive lymphatic plexus was shown in the synovial tissue from the left foreleg joint. Fixed sections showed no lymphatics in the tissue from the joint which had received injections, while an extensive

lymphatic plexus was shown in the synovial tissue from the joint of the other foreleg. Fixed sections showed the same changes on the right as described in rabbit 5. The lymph nodes draining the right knee showed no tuberculous infection in microscopic sections (fig. 9).

**RABBIT 7.**—Twelve injections of potassium iodide were made at weekly intervals into the joint cavities of the right knee and foreleg. Swelling of the joints persisted almost four weeks after the last injection. There was thickening of the joint capsule, particularly in the right knee joint, which lasted until the animal was killed nine months after the last injection. A suspension of avirulent human tubercle bacilli was injected into the right knee joint at weekly intervals for three times. One week after the last injection, the animal was killed. A 1 per cent solution of mild silver protein was injected into the joints of both forelegs four hours before the animal was killed. Smears from the synovial fluid of the right knee showed tubercle bacilli. The synovial membrane was markedly thickened on the right side. There was slight erosion of the articular cartilage, but no pannus formation. Sections from the synovial membrane of the elbows showed no lymphatics on the right side, and a fairly abundant plexus of lymphatics on the left side. Microscopic sections showed marked endothelial proliferation of the synovial membrane, with an increase in fibrous tissue in the subserous layer. Occasional lymphocytic infiltration about the blood vessels was seen. The cartilage showed slight superficial necrosis, but no change was seen in the bone or bone marrow. The lymph nodes draining the right knee and the synovial tissue of the right knee, as well, showed no evidence of tuberculous infection.

These experiments showed that the changes produced by injections of potassium iodide into joint cavities could be made relatively lasting if the injections were continued for a long enough period. Young<sup>79</sup> reported that while a single intrapleural injection of an electrolyte (strontium chloride) produced extensive epithelial proliferation in the pleura of rabbits, a second injection within eight days did not increase the amount of epithelial proliferation. A new reaction of epithelial proliferation by the pleura was not observed until the first reaction had subsided in about twenty days. This was not found to be the case in the reaction of the joint cavities of rabbits. Repeated injections of potassium iodide at weekly intervals produced a gradually increasing epithelial proliferation which was relatively commensurate with the number of injections given. The early experiments with single injections of potassium iodide showed that an almost complete restitutio ad integrum of the synovial membrane had occurred within one week. Whether a reaction on the part of the synovial membrane would have occurred with injection at shorter intervals was not determined.

The pathologic lesions that were produced in these animals were an arthritis in the sense of being an inflammation of a joint, but they did not fill the picture of the changes in the human joints as observed in atrophic arthritis (Nichols and Richardson<sup>80</sup>). The histologic

79. Young, J. S.: *J. Path. & Bact.* **34**:357, 1931.

80. Nichols, E. H., and Richardson, F. L.: *J. Exper. Med.* **16**:149, 1909.

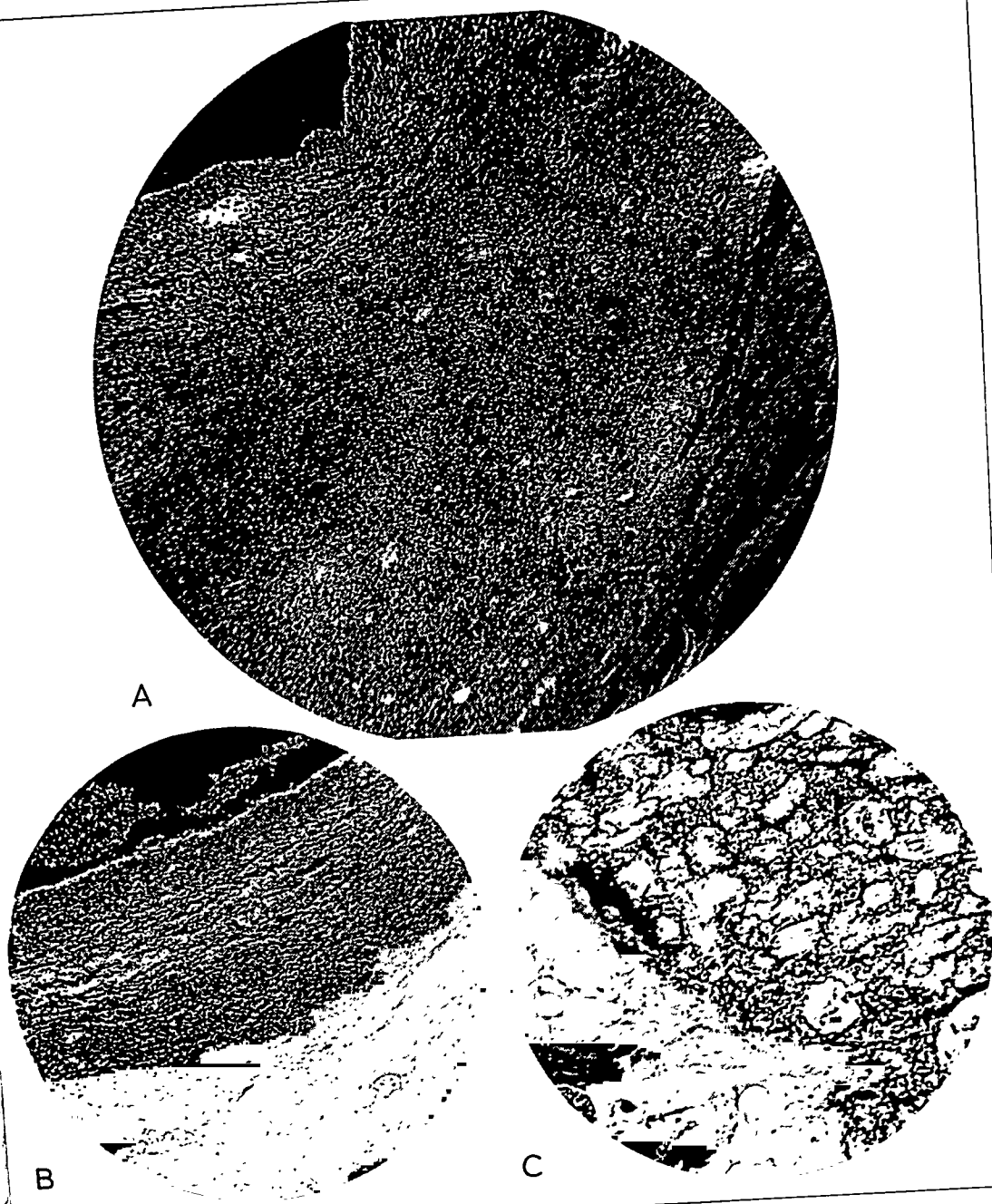


Fig. 9 (rabbit 6).—*A*, synovial membrane, right knee. There is endothelial proliferation, with marked thickening of the entire synovial membrane, fibrosis and occasional lymphocytic infiltration; reduced from  $\times 90$ . *B*, same as *A*; reduced from  $\times 70$ . Note the exudate on the synovial membrane, with some silver particles. There is no tuberculous infection. *C*, right external iliac lymph node; reduced from  $\times 125$ . There is no evidence of a tuberculous infection.

changes in the synovial membrane were somewhat similar but milder than those seen in atrophic arthritis. In no case was any pathologic change observed in the bone or bone marrow. The erosion of the cartilage and the destruction of cartilage cells were slight and superficial. There was never any pannus formation. In the cases in which repeated injections of potassium iodide alone were given, no change could be seen in the regional lymph nodes. This was to be expected, since a salt in molecular solution, so far as is known, is absorbed only by the blood vessels. It is conceivable, however, that changes in the regional lymph nodes might have occurred in the absorption of the exudate and cells thrown out against the inflammatory agent that was injected. Von Meyerding<sup>81</sup> found that in repeated infections the regional lymph nodes often showed a heightened reaction to subsequent infections, with increased dilatation of the blood vessels, swelling and proliferation of the sinus epithelium, but that otherwise there was no difference between single and repeated infections. In these cases no such reaction on the part of the lymph nodes could be made out.

No evidence of absorption of tubercle bacilli after repeated injections of tubercle bacilli into the knee joint was seen in the regional lymph nodes draining the joint cavities that had received many injections of potassium iodide. Apparently the pathologic changes in the lymphatics produced by the potassium iodide prevented the taking up of the bacilli by the lymphatics. Boquet, Valtis and Saenz,<sup>82</sup> in experiments on tuberculous infection, showed that the tubercle bacilli, after injection into normal tissues, quickly entered the lymphatics; the tubercle bacilli then passed to the blood stream and the viscera. In anything short of massive doses, the bacteria were found in the regional lymph nodes within several hours. Powlowsky,<sup>83</sup> in 1909, found that the dissemination of bacteria from joint cavities was markedly decreased when an inflammation was present in the joint cavity. He did not study the lymphatics, however. Opie<sup>84</sup> observed that acute inflammation in the peritoneal cavity of dogs retarded the absorption of bacteria injected into the peritoneal cavity and after twenty-four hours wholly prevented the absorption of such bacteria.

Both Job<sup>83</sup> and Meyer<sup>41</sup> observed, in older experimental animals, that the lymphatics appeared to be less numerous and that they could be demonstrated less readily; they also found an apparent decrease in size in the lymph nodes with increasing age. Because of this my work was done entirely with young adult animals. Job<sup>83</sup> suggested a natural involution of the lymphatic system with age similar to that observed in

81. von Meyerding, H.: *Schweiz. med. Wchenschr.* **59**:593, 1929.

82. Boquet, A.; Valtis, J., and Saenz, A.: *Ann. Inst. Pasteur* **46**:373, 1931.

83. Powlowsky, A. D.: *Ztschr. f. Hyg. u. Infektionskr.* **62**:433, 1909.

84. Opie, E. L.: *J. Immunol.* **17**:329, 1929.

the circulatory system for the blood. W. J. Mayo<sup>72</sup> stated that this apparent involution of the lymphatic tissue in elderly persons was a possible reason for the decreased virulence of infection and malignant disease in such persons.

Because the experimental work for this article had been done wholly on rabbits and because the lymphatic changes had been produced by chemicals, an attempt at corroboration of the findings was sought in human joint tissues. Healthy synovial membrane was obtained in twelve cases of infantile paralysis, in which arthrodeses were performed on joints. Grant<sup>85</sup> has recently shown that a fairly extensive synovial membrane with intra-articular folds was present even in the carpal and tarsal joints. In these cases an adequate amount of synovial tissue was always found attached to the cartilage removed at operation. The pathologic tissue studied was obtained in twelve cases: from operations for the correction of deformities in atrophic arthritis in eleven cases and from a chronically inflamed bursa in one case. Since no injections into the joints or bursa could be made, synovial tissue was studied immediately with hydrogen dioxide as previously described. Sections were also studied microscopically in fixed preparations. A brief outline of the cases and findings is given.

#### "NORMAL" SYNOVIAL TISSUE

CASE 1.—A. R., 7½ years old, had infantile paralysis of four years' duration. Tissue was obtained from the astragaloscaphoid joint. The synovial tissue treated with hydrogen dioxide showed many small lymphatics. Microscopic sections showed no pathologic changes in the synovial membrane.

CASE 2.—G. M., 9½ years old, had had infantile paralysis three years before. Tissue was obtained from the subastragalar joint. Hydrogen dioxide demonstrated a fair number of small lymphatics. The synovial membrane showed no abnormality on microscopic examination.

CASE 3.—D. G., aged 6, had infantile paralysis of four years' duration. Tissue was obtained from the subastragalar joint. The application of hydrogen dioxide to thin sheets of tissue showed many lymphatic vessels in the synovial membrane. The synovial membrane showed no pathologic lesion on microscopic study.

CASE 4.—L. W., 8 years of age, had had infantile paralysis four years before. Tissue was obtained from the subastragalar joint. Hydrogen dioxide showed a dense plexus of lymphatic vessels in the fresh synovial tissue. The synovial membrane showed no abnormality on microscopic examination (fig. 10).

CASE 5.—F. M., aged 6, had infantile paralysis of five and three-fourths years' duration. Tissue was obtained from the subastragalar joint. Many lymphatics were visible in the synovial membrane after the application of hydrogen dioxide. Microscopically, the synovial membrane showed no pathologic changes.

CASE 6.—A. R., aged 4, had infantile paralysis of two years' duration. Tissue was obtained from the subastragalar joint. Hydrogen dioxide, applied to

<sup>85</sup>. Grant, J. C. B.: *Brit. J. Surg.* 18:636, 1931.



the synovial membrane, showed many fine lymphatic vessels. The synovial membrane showed no pathologic changes on microscopic examination.

CASE 7.—T. A., aged 4, had had infantile paralysis one and one-half years before. Tissue was obtained from the subastragalar joint. Many lymphatic

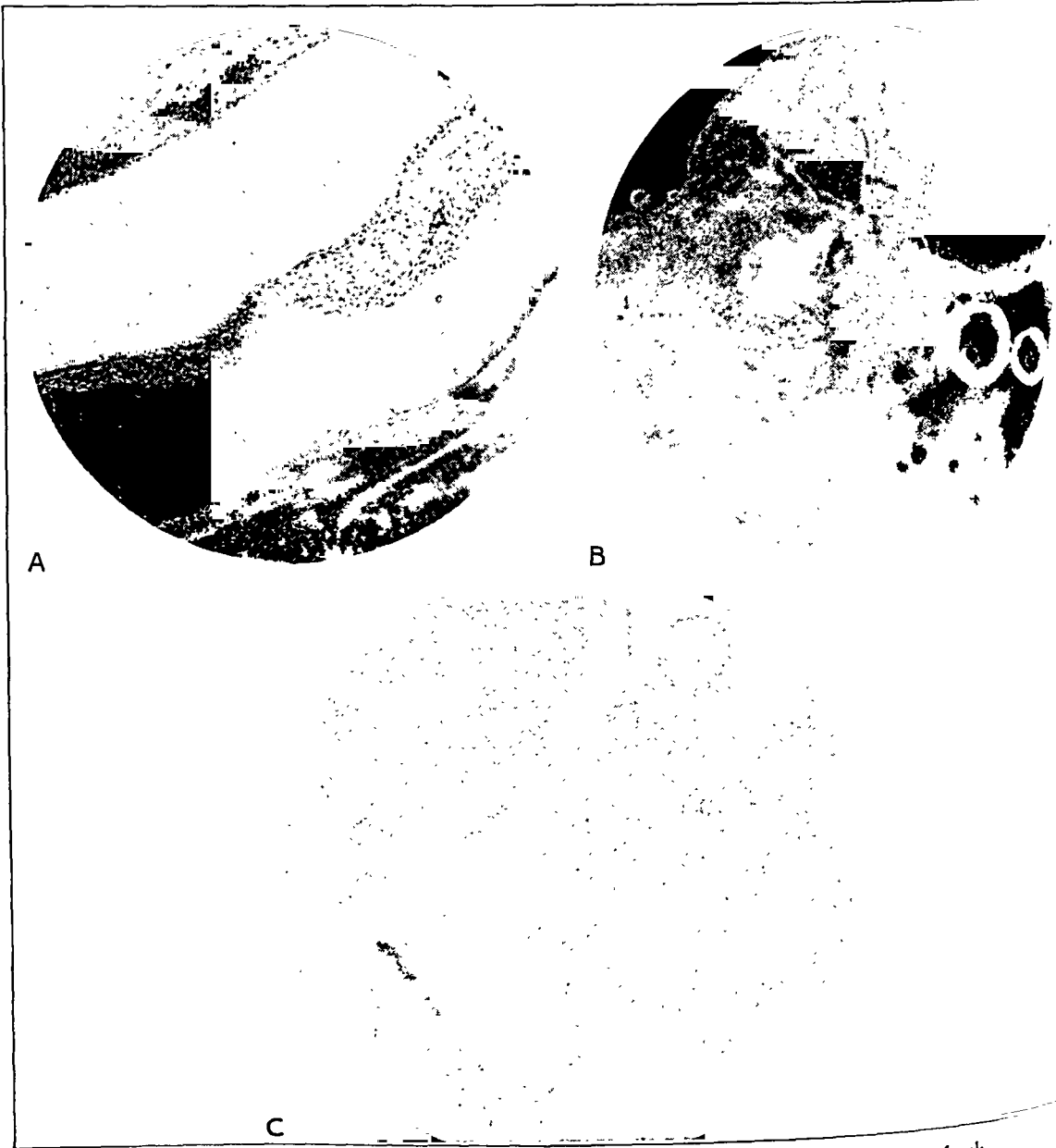


Fig. 10.—*A*, normal human synovial tissue; reduced from  $\times 80$ . *B*, fresh human synovial tissue treated with hydrogen dioxide; reduced from  $\times 80$ . Many of the lymphatics have been cut across in removing the tissue. *C*, same as *B*, showing large lymphatic vessel with branches; reduced from  $\times 240$ .

vessels were seen in the synovial membrane after the application of hydrogen dioxide. The synovial membrane showed no pathologic lesion.

CASE 8.—C. F., aged 9, had had infantile paralysis five years before. The tissue was obtained from the calcaneocuboid joint. Hydrogen dioxide showed many lymphatics in the synovial membrane. The cartilage and synovial membrane showed no pathologic lesions.

CASE 10.—G. G., aged 10, had infantile paralysis of four years' duration. Tissue was obtained from the astragaloscaphoid joint. Many lymphatic vessels were seen in the synovial membrane after the application of hydrogen dioxide. Microscopically, the synovial membrane showed no pathologic lesions.

CASE 12.—E. C., 9 years of age, had infantile paralysis of three years' duration. Tissue was obtained from the subastragalar joint. Hydrogen dioxide demonstrated many lymphatic vessels in the synovial membrane. Microscopically, the joint tissues showed no pathologic lesion.

#### DISEASED SYNOVIAL TISSUE

CASE 1.—D. S., aged 54, had chronic bursitis of the right shoulder of nine months' duration. Operation consisted in incision and curettage of an infected bursa. The tissue showed a markedly thickened bursal wall with occasional deposition of calcium, old hemorrhage in the tissues and extensive lymphocytic and leukocytic infiltration. Fresh tissue treated with hydrogen dioxide showed no lymphatic vessels.

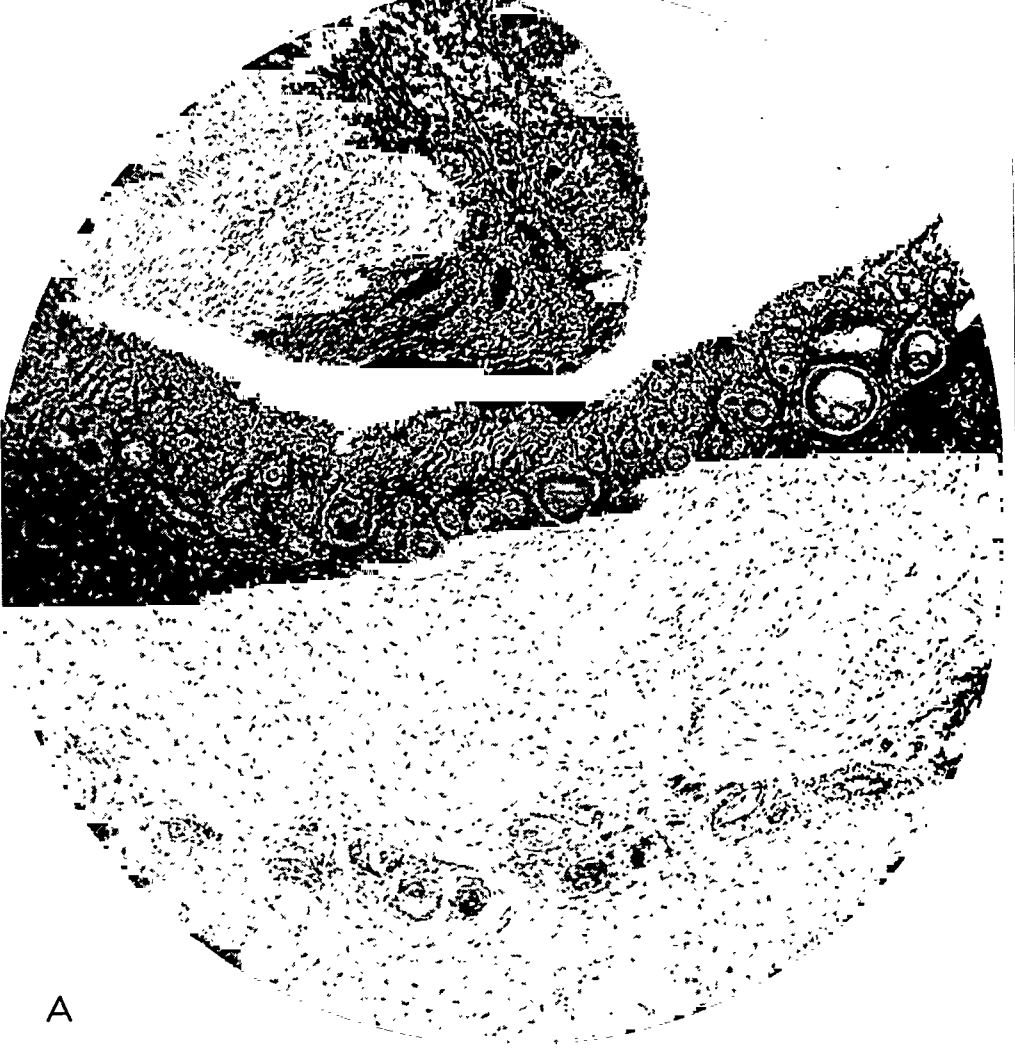
CASE 2.—E. J., aged 38, had generalized atrophic arthritis of seven years' duration. Synovectomy was performed on the right knee. The markedly thickened synovial membrane showed only one small lymphatic vessel after the application of hydrogen dioxide. Microscopic sections showed extensive venous congestion and thickening of all the layers of the synovial membrane, with occasional lymphocytic and fatty infiltration (fig. 11).

CASE 3.—M. M., aged 35, had atrophic arthritis of six years' duration. Arthroplasty was performed on the left knee. Both hydrogen dioxide and the injection of india ink into the synovial tissues demonstrated no lymphatic vessels. The synovial membrane was markedly thickened, with extensive villous formation. Microscopic sections showed a thickening of the epithelial layer of the synovial membrane, an increase in fibrous tissue in the subserous layer and occasional lymphocytes about the blood vessels.

CASE 4.—E. J. (case 2), underwent synovectomy of the left knee six months after the first operation. The markedly thickened synovial membrane showed no lymphatic vessels after the application of hydrogen dioxide. Microscopic sections showed a pathologic picture similar to that described in the tissue from the right knee.

CASE 5.—G. P., aged 16, had intermittent hydrops of the right knee of eight years' duration. Synovectomy was performed. No lymphatics were seen in the synovial membrane after the injection of india ink directly into the synovial tissues. Two short, dilated lymphatics were seen after the application of hydrogen dioxide. Microscopically, the synovial membrane showed marked venous congestion, slight thickening of all the layers and occasional aggregations of lymphocytes about the dilated blood vessels.

CASE 6.—L. M., aged 28, had atrophic arthritis of sixteen years' duration. Operation consisted in resection of the first left metatarsophalangeal joint. No lymphatics were seen in the synovial membrane after the injection of india ink directly into the tissues or by the use of hydrogen dioxide. Microscopically, the



A



B

synovial tissue showed nothing but fibrous tissue. No vestiges of the synovial endothelium remained.

CASE 7.—E. F., aged 28, had atrophic arthritis of five years' duration. Arthroplasty of the left hip was performed. Synovial tissue treated immediately with hydrogen dioxide showed no lymphatics. Microscopic sections showed thickening of the synovial membrane, with endothelial proliferation, an increase of fibrous tissue in the synovial membrane, marked congestion, slight pannus and erosion of the cartilage.

CASE 8.—J. M., aged 45, had villous arthritis of the left knee of ten years' duration. Synovectomy was performed on the left knee. Fresh synovial tissue treated with hydrogen dioxide showed one short lymphatic vessel. Microscopic sections showed a markedly thickened synovial membrane, with vascular congestion, endothelial proliferation and lymphocytic infiltration about the blood vessels.

CASE 9.—E. S., aged 7, had atrophic arthritis of five years' duration. Synovectomy was performed on the left knee. Tissues from the synovial membrane treated with hydrogen dioxide showed no lymphatic vessels. Microscopic sections showed a very thick, edematous synovial membrane, with dilatation of all the blood vessels and occasional lymphocytes about the blood vessels.

CASE 10.—C. B., aged 50, had atrophic arthritis of twenty-four years' duration. Arthroplasty was performed on the left elbow. Fresh synovial tissue showed no lymphatic vessels after the application of hydrogen dioxide. Microscopic section showed a thickened synovial membrane, with dense fibrous tissue throughout. There was no vascular congestion and no endothelial proliferation.

CASE 11.—M. B., aged 35, had atrophic arthritis of twelve years' duration. Synovectomy was performed on the right knee. Synovial tissue treated immediately with hydrogen dioxide showed two short lymphatic vessels. Microscopic sections showed a villus-like projection of the synovial membrane, with vascular congestion and fatty infiltration.

CASE 12.—C. S., aged 37, had atrophic arthritis of nine years' duration. Synovectomy was performed on the left knee. Hydrogen dioxide applied to fresh synovial tissue showed no lymphatics. Microscopic sections showed a thickened, edematous synovial membrane, with vascular engorgement and occasional accumulation of lymphocytes about the blood vessels. There was a moderate increase in fibrous tissue in the synovial membrane.

The synovial tissues obtained from human joints confirmed the findings in regard to the lymphatics as seen in the joints of rabbits. In the synovial tissues obtained from the joints of patients suffering from infantile paralysis, in whom there was no disease of the joint clinically or on microscopic examination of the tissues from the joint, the lymphatics were readily demonstrated as numerous small inflated vessels by the use of hydrogen dioxide. In the cases of atrophic arthritis or chronic bursitis only an occasional lymphatic vessel, and in most of the cases no lymphatic vessels, could be seen. So far as could be determined, no normally functioning lymphatics were present. Lymphatic vessels were demonstrated with extreme difficulty in such diseased tissue. Whether they had become collapsed by the outpouring of inflam-

matory exudate or whether they were thrombosed could not be definitely determined either by injections or in sections cut to show them in cross-section.

It is not known exactly what rôle a disturbance in function in the lymphatic vessels plays in arthritis, but there is much suggestive evidence that it is an important factor in producing decreased absorption and in preventing the subsidence of the swelling in the synovial membrane. Drinker<sup>86</sup> has suggested that in injury, blood plasma fills the intercellular spaces. This in turn encourages fibrous proliferation, if the plasma cannot readily be removed by the lymphatics. In this way the subsidence of the inflammatory reaction in tissue may be prevented, and chronic fibrous tissue may remain indefinitely if the early inflammatory exudate and cellular débris cannot be removed by the phagocytes and lymphatics. This is more than an interesting hypothesis. Since 1911, when Kondoleon<sup>87</sup> devised an operation for the treatment of elephantiasis, supposing that it was due to lymphatic obstruction, investigators have sought the cause of persistent fibrosis and edema in tissues. The recent studies of Reichert,<sup>88</sup> as well as the earlier investigations of Clark and Clark<sup>89</sup> and Matas,<sup>90</sup> have shown that chronic inflammation and lymph stasis combine to produce the pathologic and clinical picture of elephantiasis in tissues. That its persistence is due to lack of lymphatic absorption is strongly suggested by the work of Menkin,<sup>91</sup> who found that india ink or graphite did not reach the regional lymph nodes when injected into an area of inflammation. This he believed to be due to thrombosis of the lymphatics.

#### CONCLUSIONS

1. Lymphatics are present as abundant small vessels in the tissues lining joint cavities. They are most numerous just beneath the endothelial cell layer of the synovial membrane.

2. The lymphatic drainage of the joints in the lower extremity is through the so-called deep lymphatics to the popliteal, deep femoral and iliac lymph nodes.

3. Inflammation in the synovial tissues results in a decreased ability on the part of the lymphatics to absorb material larger than of molecular

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86. Drinker, C.: Lecture before Harvard Medical Society, Nov. 12, 1929.

87. Kondoleon, E.: *Zentralbl. f. Chir.* **39**:1022, 1912.

88. Reichert, F. L.: The Recognition of Elephantiasis and of Elephantoid Conditions by Soft Tissue Roentgenograms, *Arch. Surg.* **20**:543 (April) 1930.

89. Clark, E. W., and Clark, E. R.: *Anat. Rec.* **21**:127, 1921.

90. Matas, R.: *Am. J. Trop. Dis.* **1**:60, 1913.

91. Menkin, V.: *J. Exper. Med.* **53**:647, 1931.

size. An apparent obliteration of the lymphatic vessels occurs when the inflammatory process is sufficiently severe or long continued.

4. With the subsidence of the inflammatory reaction, the lymphatics are again seen in their usual size and distribution, and absorption of particulate substances is again observed by the lymphatic vessels.

5. Persistent inflammation in synovial tissues is dependent to a certain extent on the nonfunction of the lymphatic vessels.

# WOUND OF THE SUPERIOR VENA CAVA TREATED BY SUTURE

## REPORT OF A CASE

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Wounds of the great vessels within the mediastinum are rare and are usually rapidly fatal. When such a vessel is injured outside the pericardium, the signs and symptoms are those of massive intrathoracic hemorrhage; whereas if the intrapericardial portion is injured, cardiac tamponade is apt to result. No case of repair of such a wound can be found in the literature. Because of this fact and because of the importance of recognizing the possibility of such a wound so as to make an incision which will give adequate exposure, the following case is reported.

## REPORT OF CASE

*History.*—S. B., a colored man, aged 34, was admitted to the Saint Philip Hospital, on Feb. 1, 1932, complaining of a stab wound of the right side of the chest and incised wounds of the left wall of the chest and the left hand. He had received the wounds about thirty minutes before admission to the hospital.

*Examination.*—On examination the patient was apparently in a state of profound shock. There had been little external loss of blood, and there were no physical signs of massive internal hemorrhage. The stab wound in the right side of the chest had penetrated the third costal cartilage 1 cm. to the right of the sternum. The wound in the left wall of the chest was at the level of the eighth rib in the posterior axillary line and obviously had not penetrated the pleural cavity. The wound on the left hand was of little importance. There was flatness at the base of the right lung posteriorly, indicating a moderate collection of fluid in the right pleural cavity, but there was no evidence of pneumothorax. Auscultation over the pericardial area showed the heart sounds to be distant and muffled, but percussion did not reveal an appreciable enlargement of the area of pericardial dullness. Because of the distant muffled heart sounds and the extreme circulatory failure, which was out of proportion to the loss of blood, it was thought that the patient had a wound of the heart; hence immediate operation was advised. Because of the fact that the wound was located in the upper portion of the chest, it was thought that it had probably entered the right auricle; the incision was made on the right side.

*Operation.*—With the patient under local anesthesia (a 0.5 per cent solution of procaine hydrochloride), a curved incision was made over the second costal

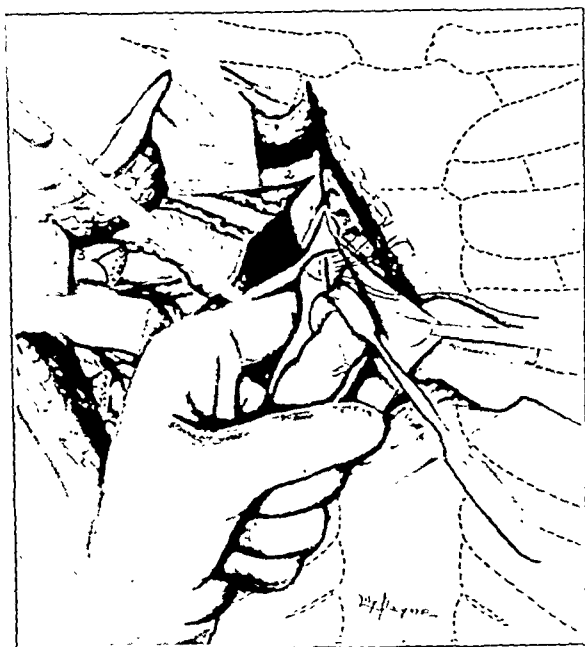


Fig. 1.—Drawing showing the excellent exposure of the right auricle and the intrapericardial portion of the superior vena cava and the method used to control hemorrhage.



Fig. 2.—Photograph taken twenty-two days after operation, showing the location and appearance of the incision.



cartilage near the sternum and carried downward and outward to the upper border of the fifth rib and out along the rib to the anterior axillary line. The stab wound was excised. The pectoral muscles were divided and retracted upward and outward, and the second, third and fourth cartilages exposed. The third and fourth cartilages were excised and the second cartilage divided and retracted upward. The internal mammary vessels were ligated and divided. The right border of the sternum was rongeured away between the second and fifth cartilages. The right pleura was found to extend unusually far to the left, so the pleura was opened; about 500 cc. of blood was found. The pericardium was tense, and obviously contained a large amount of blood. A wound about 1 cm. in length was found in the right side of the upper portion of the pericardial sac. This wound was enlarged and the pericardial cavity widely exposed, whereupon dark blood gushed from the upper portion of the sac. Further examination revealed a wound 1 cm. in length in the anterior wall of the superior vena cava immediately above the right auricle and partially covered by the right auricular appendage. The hemorrhage was partially controlled by passing the index finger of the left hand posterior to the vena cava, and the wound was closed with three interrupted mattress sutures of silk. The pericardium was not closed. The pleura was approximated with interrupted sutures of chromic catgut, the muscles with chromic catgut and the skin with silk. During the closure of the wound in the vena cava, the patient's heart began to fibrillate and continued to do so for about thirty minutes. It was thought that this was probably due to traction in the region of the sino-auricular node.

*Postoperative Course.*—At the time of the patient's return to the ward the systolic blood pressure was 90 mm. of mercury and the pulse was of good volume but still irregular. On the following day, the systolic blood pressure remained around 100 to 110 mm. of mercury; the temperature remained around 100 F., and the pulse rate ranged between 120 and 135. The second day after operation the temperature rose to 104 F. and the pulse rate to 140; both remained elevated for four days. At this time roentgen examination showed areas of increased density in the lower lobe of the right lung and in the left costophrenic angle, which were interpreted as areas of atelectasis. A moderate collection of fluid accumulated in the right pleural cavity, and there was some displacement of the mediastinum to the left. The leukocyte count made on the second day after operation, at the time of the marked elevation of temperature, was 14,700, the hemoglobin, 45 per cent and the polymorphonuclears, 80 per cent; at this time the blood pressure was 150 mm. of mercury systolic and 120 diastolic. The blood pressure remained high for about four days and then gradually fell to 120 mm. of mercury systolic and 85 mm. diastolic. Unfortunately, electrocardiographic tracings were not made until the heart had regained a normal rhythm; several which were made during the convalescence were normal.

At the time of the patient's discharge from the hospital, on March 3, thirty-two days after operation, the general condition was favorable; the pulse was regular and of good volume; the wound had completely healed, and examination of the heart showed no abnormal findings in regard to size or to function.

## CLINICAL CONSIDERATION OF GASTRIC ULCER AND CARCINOMA

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It is a debated question among pathologists whether a high or a relatively low percentage of gastric ulcers undergo carcinomatous transformation. McCarty<sup>1</sup> said that 68 per cent of resected ulcers are associated with carcinoma; Wilensky and Thalhimer<sup>2</sup> found that 1 or 2 per cent of ulcers develop into carcinoma. In this presentation I shall deal with the clinical aspects of the problem and not enter into the histopathologic debate. One must decide whether medical treatment is ever justifiable or whether the patient should be subjected at once to subtotal gastrectomy. In view of the difference of opinion among pathologists, one is justified in basing a clinical decision on the number of ulcers, diagnosed clinically and roentgenologically, that subsequently manifest carcinomatous changes. One must, of course, make a differential diagnosis between ulcer and carcinoma, and this is frequently difficult when the latter is in an early stage. Friedenwald and Baetzer<sup>3</sup> in 1913 called attention to the use of roentgen examination in the determination of the degree of healing of an ulcer, which cannot be as certainly determined in any other way. In the borderline cases it may be necessary to resort to a Sippy regimen before the roentgenologist can commit himself to a decision between ulcer and early carcinoma. In early carcinoma medical treatment rarely abolishes pain; the lesions are not diminished on subsequent roentgen examination and may actually have increased in size. It is not fair always to expect a roentgenologist to commit himself to a positive statement on one examination of the gastro-intestinal tract any more than to expect a clinician to make a positive diagnosis from a physical examination without the aid of laboratory data; but if a competent roentgenologist has the opportunity to base his diagnosis of ulcer on a second examination after a brief Sippy regimen, subsequent diagnosis of carci-

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1. McCarty, Wm. C.: Surg., Gynec. & Obst. **10**:449 (May) 1910.
2. Wilensky, Abraham O., and Thalhimer, William: Ann. Surg. **67**:215 (Feb.) 1918.
3. Friedenwald, J., and Baetzer, F. H.: Tr. A. Am. Physicians **28**:157, 1913.

noma is seldom made. Buckstein<sup>4</sup> stated that he had rarely seen an ulcer diagnosed by himself which at a subsequent date he had been able to demonstrate to be a carcinoma. It is admitted that a roentgenologist with limited experience in gastro-intestinal work may have considerable difficulty in differentiating the two lesions. Balfour<sup>5</sup> in 1930 reported 100 cases of gastric ulcer in which gastro-enterostomy was done without excision of the ulcer. These patients were followed for a ten year period, and only 6 of them died from carcinoma during that time; approximately 80 per cent were symptomatically well. Balfour admitted that the lesions were so large and fixed that any procedure other than gastro-enterostomy would have carried a high mortality, and it was questionable at the time of operation whether benefit could be derived from gastro-enterostomy without excision of the ulcer. The clinical observations of Balfour are in keeping with Ewing's<sup>6</sup> conclusion, from pathologic observations, that about 5 per cent of gastric ulcers develop into carcinoma.

My associates and I observed 460 peptic ulcers in the gastro-enterologic clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital from January, 1928, to January, 1932. There were 332 nonoperative cases and 128 operative cases. In the nonoperative cases there were 280 duodenal, 31 gastric, 14 pyloric and 7 double (a lesion in both the stomach and duodenum) ulcers. It is interesting to note that we have not seen a case clinically in which carcinoma has developed from an ulcer. The insidiousness of the onset of carcinoma of the stomach was well illustrated in the 15 cases that we observed during this time; the lesion was far advanced in all when the patients were admitted. Alvarez,<sup>7</sup> in 1931, reported 41 cases of carcinoma of the stomach in physicians and called attention to the fact that gastric ulcer is a frequent forerunner of cancer; but in 20 of his cases the shortness of the history testified again to the insidiousness of the onset. If the neoplasms were accompanied by the pain characteristic of gastric ulcer, these physicians would have been astute enough to recognize the symptoms of ulcer and would have received either medical or surgical treatment.

There is an important question that must be answered if carcinoma bears any relation to ulcer: Why does one not see carcinoma of the duodenum arising from duodenal ulcer? It is known that primary

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4. Buckstein, Jacob: Personal communication.

5. Balfour, Donald C.: Results of Gastro-Enterostomy for Ulcers of the Duodenum and Stomach, *Ann. Surg.* **92**:558 (Oct.) 1930.

6. Ewing, James: *Ann. Surg.* **67**:715 (June) 1918.

7. Alvarez, Walter C.: How Early Do Physicians Diagnose Cancer of the Stomach in Themselves? A Study of the Histories of Forty-One Cases, *J. A. M. A.* **97**:77 (July 11) 1931.

carcinoma of the duodenum frequently occurs, and carcinoma in this portion of the small intestine is more commonly encountered than in the remainder of the entire small intestine. Duodenal ulcer in our series occurred in a ratio of about 8:1 in comparison with gastric lesions. With the frequency of duodenal lesions and the relative frequency of primary carcinoma of the duodenum it would seem that the ulcer-carcinoma sequence would occasionally be encountered, but a careful review of the literature<sup>8</sup> on this subject failed to reveal a definitely proved case. The transformation of the epithelial cells at the pylorus is gradual, and there is no abrupt change from the pylorus to the duodenum; this is an added reason why carcinoma should develop in duodenal ulcers.

The following cases will illustrate the misunderstanding that frequently arises in evaluating the life cycle of an ulcer unless one has a complete history and clinical record with the roentgenologic findings of the case.

#### REPORT OF CASES

CASE 1.—A man, aged 46, was admitted to the hospital on Oct. 24, 1927; he had been complaining for six months of pain in the stomach before and after meals, which was not relieved by food but was alleviated by sodium bicarbonate. During the past three months he had lost from 15 to 20 pounds (7 to 9 Kg.). Roentgenologic examination of the gastro-intestinal tract on October 27 revealed carcinoma of the pylorus, with one third of the motor meal retained at the end of six hours. Operation on October 29 revealed an ulcer of the first portion of the duodenum,  $\frac{1}{2}$  inch (1.27 cm.) distal to the pyloric vein; posterior gastro-enterostomy was done. The patient was followed in the gastro-enterologic clinic; he was symptom-free until April, 1930, when the abdomen became distended and he began to vomit, with loss of weight. Early in July he became jaundiced, and was readmitted on July 25. Roentgenologic examination on June 25 revealed carcinoma of the pylorus. At operation, on July 31, a carcinoma of the pylorus was found with general abdominal metastases and biliary obstruction; cholecystojejunostomy was done, but the patient died on August 1.

From the history, results of roentgen examination and subsequent course there is nothing to indicate a duodenal ulcer except the operator's findings.

CASE 2.—A man, aged 61, was admitted to the hospital on June 17, 1930. The chief complaint was pain in the epigastrium for two months. There had been no serious illness or surgical operations. The patient smoked from twenty to thirty cigarets daily and drank occasionally, usually whisky. He stated that he had been well until two months before, when he began to suffer from pain in the epigastrium and eructations. The pain began in the right upper quadrant of the abdomen near the midline and radiated to the back on both the right and the left side of the spine, extending as high as the scapula. It came on about four hours after breakfast and about the same time after lunch and also awakened him about 2 a. m. The pain was relieved by alkalis and somewhat by pressure over the epigastrium. He had never vomited, but had always been constipated; during the past two

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8. Hinton, J. William: Does Carcinoma of the Duodenum Ever Arise from Duodenal Ulcers? *Am. J. M. Sc.* **181**:843 (June) 1931.

months he had noticed tarry stools. His appetite was good, but he was afraid to eat as it caused pain. During his illness he had lost from 15 to 18 pounds (7 to 8 Kg.).

Physical examination gave negative results except for abdominal findings. No definite mass was palpated, but there were localized tenderness in the mid-epigastrium and slight costovertebral tenderness. The clinical impression was that the condition was carcinoma of the stomach. On June 18 urinalysis gave negative results; the white blood count was 10,000, with 55 per cent neutrophils; the red blood count was 3,500,000; there was 55 per cent hemoglobin; the nonprotein nitrogen was 35 mg. per hundred cubic centimeters, creatinine was 2.4 mg., and sugar 90 mg; the Wassermann test was negative. After four gastro-intestinal roentgen examinations, a diagnosis of ulcer of the first portion of the duodenum was made with no evidence of neoplasm of the stomach and with no six hour residue. On June 24, a barium enema showed no organic lesions of the colon. On June 28, the gallbladder was not clearly defined by cholecystography. On June 26 this note was made by the house physician: "Patient is suffering considerable pain at night, which causes him to awaken about 2 a. m., pain being in midepigastrium and radiating to the back. The patient has complained of pain every night since admission. Impression: penetrating ulcer of the duodenum." Surgical consultation was held on July 3. The patient had been vomiting for twenty-four hours and was emaciated, complaining of severe abdominal pain which radiated to his back. Examination did not reveal any abdominal masses, but there were localized tenderness in the midepigastrium and costovertebral tenderness. The diagnosis was penetrating ulcer of the posterior wall of the duodenum, associated with chronic pancreatitis.

The patient was given a 3 per cent dextrose hypodermoclysis daily and a transfusion the day before operation. He was operated on on July 11 by Dr. W. T. Doran, under spinal anesthesia. A mass was found involving the pylorus and was deemed to be malignant, but, as it was firmly fixed, glands were not obtainable for biopsy; no nodules were felt in the liver. Owing to the patient's serious condition, posterior gastro-enterostomy was then done without clamps. The patient declined in spite of supportive measures and died on July 20, 1930.

The observations at autopsy (reported by Dr. D. Symmers) were as follows: "In the first portion of the duodenum there is a hard, nodular, faintly cream-colored mass which is centrally ulcerated and which measures 6.5 cm. in diameter. It projects into the lumen of this portion of the intestine in somewhat mushroom fashion, and appears to be directly continuous with the outer 2 or 3 cm. of the head of the pancreas which is enlarged and increased in consistence. The rest of the head of the pancreas and, in fact, the balance of the organ as a whole are of normal consistence. Microscopic examination of tissue removed from various parts of the tumor shows the presence of a richly cellular and abundant connective-tissue stroma, scattered through which are innumerable acini of variable shapes and sizes. The individual acinus is lined by a single row of high cuboidal or low cylindrical epithelium, the cells being arranged on their basement membrane in more or less regular fashion. In some instances, however, the cells are heaped up into rows of two or three, while in other instances they may be so abundant as completely to fill the lumen, and thus to appear as a solid mass of cells. Although the histology of the tumor is characteristic of the cylindrical-cell adenocarcinoma springing from the pancreatic ducts and reproducing them in typical fashion, the presence of a large mushroom-like tumor projecting itself into the lumen of the duodenum and simulating a primary growth of that region is, in my experience at least, a most unusual finding, and constitutes perhaps, the outstanding feature of this particular case."

*Comment on Cases 1 and 2.*—Case 1 is apparently one of a primary carcinoma of the duodenum that was mistaken for a duodenal ulcer; case 2 comes nearer to establishing proof that a duodenal ulcer may develop into carcinoma than has any case yet reported. When the growth was carefully studied, however, it was thought in all probability to have arisen from the pancreas and to have invaded the duodenum secondarily.

CASE 3.—A man, aged 42, was admitted to the clinic on June 30, 1928, having complained of pain in the epigastrium for the past year and a half. This pain had been coming on two hours after meals, and was occasionally relieved by the taking of food. It had spontaneously disappeared at intervals of from several weeks to several months. In January, 1928, he had been operated on for an epigastric hernia which was thought to be the cause of his abdominal pain, as the results of two roentgenologic examinations of the gastro-intestinal tract had been pronounced negative, but the pain was not relieved. One month after being discharged from the hospital he was reexamined roentgenologically, with negative findings. Examination on June 18 revealed a pyloric ulcer, and the patient was admitted for treatment. He was put on an ambulatory Sippy regimen and given nonspecific streptococcus vaccine every week, the dose being increased to 1.5 cc. He progressed fairly satisfactorily after the first two months of treatment and was greatly improved symptomatically six months after treatment was started. Roentgenologic examination on May 27, 1929, revealed an ulcer at the pars pylorica and pars media on the lesser curvature, but the pyloric ulcer was not found. This examination was repeated one week later, and the ulcer which was originally reported at the pylorus was pronounced healed. The patient left the city one month later and began having increased epigastric distress. He was admitted to St. Vincent's Hospital, Worcester, Mass., and roentgen examination revealed a gastric lesion at the junction of the pars media and the pars pylorica. He was operated on on July 18, 1929, with the following findings: "An ulcer with the thick rim and crater the size of half an English walnut was found at the middle of the lesser curvature with large indurated glands in the lesser omentum, which were firmly attached. The lesion was considered malignant and inoperable; so an anterior gastroenterostomy was done."

The patient returned to the clinic two months after being discharged from the hospital and was followed until Dec. 4, 1930. During this time he had remained in excellent general condition, but roentgenologic study of the stomach revealed a carcinoma which was progressing in size. However, the patient was maintaining his weight when last seen.

*Comment.*—This case illustrates two very important points: (1) the difficulty of demonstrating the ulcer which was undoubtedly present when the three negative roentgenologic examinations were made, and (2) the fact that a carcinoma may develop in a stomach which has been the site of an ulcer, but quite independently of the ulcer.

CASE 4.—A man, aged 38, was admitted to the clinic in June, 1928, complaining of abdominal pain and stating that he had been treated for ulcer of the stomach. The past history was unimportant. The patient stated that in 1922 he was having pain after meals, which was growing progressively worse. At that time he entered the New York Hospital and was examined roentgenologically and treated by means of diet for four weeks. Roentgen examination at that hospital revealed a duodenal

ulcer. Since then he had been under the care of numerous physicians and had obtained some relief, at intervals, but his condition had gradually become worse. Roentgenologic study of the gastro-intestinal tract on April 20, 1928, showed that the stomach was normal but that there was an ulcer of the first portion of the duodenum with partial obstruction. The patient, after being put on a bland diet and given nonspecific streptococcus vaccine, showed definite improvement. Roentgen examination was repeated at four different times during the treatment; at all of these examinations the stomach was found normal and the lesion was demonstrated in the duodenum. In July, 1929, he returned to his native country, Poland, for three months, symptomatically greatly improved but not entirely well. While away he began to have pain in the stomach, and he returned to the clinic in November, 1929, at which time he had lost 20 pounds (9 Kg.) in weight and was still complaining of pain. Roentgen examination revealed a carcinoma of the stomach at the junction of the pars media and pars pylorica. At operation, in December, 1929, a carcinoma was found involving the entire stomach from the esophagus to the duodenum. It apparently arose at the junction of the pars media and pars pylorica. A gland was taken for biopsy, which revealed adenocarcinoma.

**CASE 5.**—A man, aged 52, was admitted to the clinic on July 2, 1930, having complained of pain after meals for four or five years. Roentgen examination on June 25, 1930, revealed an ulcer at the junction of the pars media and the pars pylorica. The patient was given an ambulatory Sippy diet and Saunders vaccine and became symptomatically well within two months. On Oct. 1, 1930, roentgenologic study of the stomach gave negative results. On Jan. 16, 1931, the results were again negative, but the patient had some pain in the abdomen. On April 10, however, he complained of definite pain after meals, and roentgen examination on May 6, 1931, revealed a deformity at the pyloric end of the stomach suggesting carcinoma. Reexamination on June 4 revealed a definite carcinoma of the stomach. Operation was performed on June 8. An indurated area was found on the posterior portion of the pylorus. The stomach was freely movable, and there was no evidence of involvement of the liver. The gastrocolic and gastrohepatic omenta were freed, and the duodenum was resected and closed with three layers of Pagenstecher sutures. About one half of the stomach was then excised, and the jejunum was brought through the transverse mesocolon and anastomosed to the lower end of the stomach, according to the Finsterer technic, with two rows of no. 1 chromic catgut posteriorly and three rows anteriorly. After the anastomosis had been completed, the opening in the transverse mesocolon was sutured to the stomach with three Pagenstecher sutures. The anastomosis between the stomach and jejunum lay easily without tension. The abdomen was closed in anatomic layers.

When the specimen was inspected an ulcerated area was found on the pylorus which could easily be an ulcer or an early carcinoma, but my impression was that it was purely inflammatory. On the lesser curvature, about 2 inches (5 cm.) from the other lesion, an indurated area was found which gave every appearance of being a healed ulcer, and this apparently was the first lesion from which the patient had suffered. It had entirely healed under medical treatment, the pyloric ulcer being of recent origin. The pathologic report was peptic ulcer without evidence of malignancy.

*Comment.*—This case revealed an ulcer at the junction of the pars media and the pars pylorica which healed under medical treatment; the ulcer at the pylorus was a separate lesion and was mistaken for an early carcinoma at roentgen examination. Histopathologic examination

of the ulcer failed to reveal any evidence of carcinoma, and even though it had been proved to be carcinoma it would not have borne any relation to the original lesion of the pars media and the pars pylorica.

#### SUMMARY

It is apparent that there is a great diversity of opinion among pathologists as to the percentage of gastric ulcers in which carcinomatous changes develop. If one follows cases over a long period, as Balfour did, it is seen that only a small percentage of patients actually die of carcinoma when the gastric lesion is not removed, although in Balfour's cases the lesion was of considerable size at the time of the operation. The cases reported from our clinic illustrate how unfair it is to draw the conclusion that carcinoma has arisen in an ulcer for which the patient had previously been treated, unless the original roentgenologic findings have been obtained for review and comparative study. It is my feeling that carcinoma rarely develops from a gastric ulcer, and that conservative treatment may be employed without fear of carcinoma developing from an ulcer except in a small percentage of cases. I would maintain that a gastric ulcer is not a true indication for subtotal gastrectomy, if the argument for this procedure is prophylaxis against carcinomatous transformation in the existing gastric lesion.

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# A REVIEW OF UROLOGIC SURGERY

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*Stone*.—Violle<sup>1</sup> stated that of the three kinds of urinary stones, oxalatic, uretic and phosphatic, the phosphatic stones are by far the most common. The former two types are influenced by general metabolic conditions, but this is not always true of phosphatic lithiasis, since local conditions may of themselves suffice to produce it. Phosphatic lithiasis may complicate both the other types or may replace them. Then a slow and rather restrained lithogenic process may be transformed into a rapid and active one. Two conditions are necessary for such lithiasis: precipitation and the compaction of the substance precipitated. These processes occur at two different times.

Precipitation is in great part a function of urinary reaction, and is chiefly a question of hydrogen ion concentration. For precipitation a certain amount of calcium diphosphate must be present, which cannot exist unless the  $p_H$  rises above 6. When the urine is hyperacid, it contains monometallic phosphates, but very little of the bimetallic phosphates. The monometallic phosphates are very soluble; hence for  $p_H$  on the acid side of neutral there is no possibility of precipitation of phosphate. But as acidity diminishes, bimetallic phosphorus increases,

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1. Violle, P. L.: Contribution à l'étude de la lithiase phosphatique urinaire, Presse méd. 40:236 (Feb. 13) 1932.

and this may be only slightly soluble, depending on the quality of the phosphates. If they are disodic or dipotassic, they are not harmful, but if they are alkaline, for example, dicalcic, they are only slightly soluble. The danger zone for dicalcic phosphaturia begins above  $p_H$  6, which the author calls the zone of calcium phosphate lithiasis. The  $p_H$  of the urine varies greatly in twenty-four hours. When it is in the danger zone, little variation from the usual dietary regimen, such as slight indigestion, is sufficient to cause sudden precipitation. Lactescent urine may form in the kidney, but especially in the bladder; hence phosphocalcic lithiasis is chiefly a vesical lithiasis. In the bladder urine rich in calcium may be mixed with hypo-acid urine; then immediate precipitation occurs. Sodium diphosphate, by double decomposition with neutral and soluble calcium salts, forms insoluble calcium diphosphate.

Alkalinity of the urine may be due to septic or aseptic causes. The former are well known, the latter less so. Aseptic causes are a vegetarian diet and hyperchlorhydria. The hyperchlorhydric subject normally has acid urine one hour before eating. But after eating, the gastric hypersecretion places the urine in the danger zone of phosphocalcic precipitation; the urine is at its limit of solubility, and with one step more passes the mark. This step is taken when the alkaline wave appears about four hours after a meal has been ingested following the crisis of hyperchlorhydria. At the time of the crisis, the urine is still clear; half an hour later it is flocculent, with flakes of phosphorus in suspension.

The precipitation has this special feature. Owing to its prolongation it occurs not only in the bladder but in the kidney, as is shown by pain in the kidney experienced by patients at certain hours of the day or night, corresponding to an elevated  $p_H$ . The pain may be acute, like renal colic, and be accompanied by the emission of phosphocalcic flakes or even small calculous concretions. On the other hand, the pains and flakes disappear together so that one fact becomes evident; namely, that in a number of subjects with hyperchlorhydria, phosphocalcic precipitation occurs at the level of the kidney.

The cause of lithogenesis following precipitation is inflammatory irritation in septic cases and crystals in aseptic cases. Crystals are rarer than in oxalate or uric acid lithiasis. There is one variety of calcium phosphate lithiasis associated with profound disturbance of calcium metabolism; namely, that in which the calcium in the blood is increased. The cause must lie in avitaminosis or in a functional disturbance of the parathyroid glands. At any rate, irritation by crystals provokes desquamation and an exaggerated mucoserous secretion, to which erythrocytes may be added. This exudate and desquamation form a sort of agglomeration with the precipitated salts. Thus microbes, erythrocytes, leukocytes and cellular debris are points around which precipitated salts may

collect. Almost always in the center of calculi organic elements may be found.

Treatment consists in rendering the urine sufficiently acid to prevent precipitation, in giving as little calcium as possible in the diet, in prescribing no organic acids and in the use of muscular exercise. If the urine is antiseptic treatment should be continued, and the hydrogen ion concentration determined frequently.

[COMPILERS' NOTE.—Violle's explanation of the cause of phosphatic lithiasis closely parallels that of Eisenstadt, who stated his belief that phosphate stone arises chiefly from the effect of urea-splitting organisms which raise the hydrogen ion concentration of the urine to a high alkaline level. Eisenstadt consistently found bacteria in the nucleus of phosphatic stones examined by the method of Hellström. This coincides with the views advanced by Violle.

It is felt, however, that considering the whole range of chemical precipitates involved in various types of calculi and the wide variations of the hydrogen ion concentration of the urine in health and disease, when concomitant lithiasis is not present, some other factor must be sought in the formation of stone. The present tendency to overlook a disturbance of the protective colloids of the urine as a factor in lithiasis is untenable if one remembers the work of Lichtwitz and Schade in producing calculi *in vitro*, and the experiments of Keyser who produced experimental calculi in animals and traced the morphologic relationship of their component crystals to the urinary colloids.]

Beer<sup>2</sup> stated that before analyzing the problem of recurrent calculi in the urinary tract, one must distinguish between genuine recurrences and false recurrences; the latter are due to overlooked smaller or larger fragments which have been allowed to remain in the kidney following what appeared to be complete surgical evacuation. The modern development of the surgery of renal calculi, controlled by roentgenologic examination of the exposed kidney in the operating room, has made it possible to empty the kidney more completely than before this procedure was introduced. Fluoroscopic control of the exposed kidney has proved less satisfactory than photography on a small film with an intensifying screen. Beer further explained that in addition to this control in the operating room, it is customary to take a series of flat roentgenograms before the patient is discharged from the hospital, in order to confirm the findings in the operating room. He stated that if all stones or fragments of stone are not removed, and unless one is certain that the kidney is emptied, consideration of the incidence of true recurrence is of questionable value. However, if all stones have been removed and

2. Beer, Edwin: *Ann. Surg.* 96:136 July) 1933.

in the course of months or years a stone develops in the kidney, then it is a true recurrence.

If infection sets in, a totally different type of stone forms in the urinary tract, kidney or bladder, or in the gallbladder. In these observations concerning the urinary bladder, stagnation of urine seems to be the clue to the formation of stones, and it is likely that similar stagnation in the pelvis and calices of the kidney may contribute to the formation of primary uric acid, oxalate or phosphatic stones. As a result of infection, stones of earthy phosphates are most likely to develop, and the problem is to control both stagnation and infection in the kidney, if recurrent stones are to be avoided. Beer found that in the lowest calix, perhaps owing to the upright position of human beings, stones seem to form more commonly than in the other calices, either as primary stones in the calix or as extensions from a pelvic stone.

It is Beer's opinion that if deformity of the kidney and poor drainage are not controlled, dietary measures for controlling recurrence of stones seem to be of little value. Uric acid calculi, which are present in between 6 and 10 per cent of all cases, probably can be controlled by diet. Phosphatic primary stones possibly can be controlled by making the urine highly acid. Oxalate stones cannot be prevented with any regularity by a diet low in oxalate, although it is well worth while to advise the patient to avoid foods rich in oxalates. Cystine stones also are hard to control, although it has been suggested by some observers that alkalinization may prevent reformation after removal of such stones. Recurrent stones in infected kidneys are much more difficult to control; even with pelvic lavage and the use of antiseptics one cannot with any regularity control reformation. However, at operation, free drainage must be established from the kidney, and if possible, if a dilated calix is found, for instance in the lower pole, this pocket should be obliterated either by using mattress sutures or by resection of the lower pole if the calix is very large. It is doubtful if nephrostomy with irrigation is of value in preventing recurrence in the presence of infection. It seems more advisable to rely on natural diuresis and the use of forced fluids to attempt to wash out the renal cavity than to rely on occasional irrigation through the cortex or through the ureteral catheter. However, in some cases in which much sand has been encountered, postoperative irrigation of the kidney through the nephrostomy tube with weak antiseptic solutions, such as hydrochloric or acetic acid, may dissolve some of the earthy phosphates and thus delay recurrence of stone.

Beer states that results of experiments with phosphatic deposits following cystotomy have been much the same. The experiments are difficult to control unless the urine is acid, and it has been found that the best acidifier is 10 grains (0.64 Gm.) of boric acid and sodium benzoate with 10 grains of methenamine, to which ammonium chloride

can be added as required. In addition, in some of the more obstinate conditions, hydrochloric acid and acetic acid in solution as high as 1:1,000 or a buffer mixture containing the sodium and calcium salts or lactic acid have been used successfully.

Randall<sup>3</sup> explained that among the various urinary concretions which are known to occur, there is some understanding of causative factors of only one variety. This is the so-called earthy or triple phosphatic stone. It has been recognized for some time that certain bacteria have a limited range of chemical reaction in which they normally thrive. Nowadays all bacteriologic mediums are titrated to determine their hydrogen ion concentration in order to cultivate organisms successfully. If their cultural habitat is changed in this one factor, bacteriostatic or bactericidal action is obtained. Surgeons have long trusted to iopax as a urinary antiseptic, and in order to insure the generation of formaldehyde, an acid medium is necessary. For this purpose, acidifying drugs are given by mouth to produce an acid urine.

There is a recognized group of organisms which have the power of breaking down urea in the urine with the formation of ammonia; *Staphylococcus*, certain strains of *Bacillus coli*, *B. subtilis* and *B. alcaligenes* are characteristic of this group. They create alkaline urine by their ability to split urea, and having created their ideal habitat, they thrive therein. With the formation of alkaline urine, there is a resultant precipitation of the alkaline inorganic salts of calcium, magnesium and ammonium, of which the characteristic phosphatic calculi are formed. Here, Randall stated, is a clear insight into this probable etiologic factor. Such phosphatic calculi have three characteristics: (1) They are the most rapid-growing stone seen; (2) once their deposition starts, they are rarely superseded by the precipitation of other urinary salts, and (3) they are the stones formed by the chronic stone-producers.

Randall undertook in his clinical work so to change the reaction of the urine that bacterial growth and precipitation of phosphates would be inhibited or prevented.

Randall first applied such measures in the treatment of patients who had undergone cystotomy, and there was subsequent drainage through suprapubic fistulas. These patients had undergone prostatectomy, and their wounds had broken down. The wounds in these cases seemed to be related to alkalinization of the urine. At their worst they presented ugly, sloughing, gangrenous sores, on the walls of which, and even on the abdominal skin, there were likely to be encrustations of phosphates. Such encrustations could be dissolved by topical application of a 5 or 10 per cent solution of phosphoric acid, and the wound

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3. Randall, Alexander: Recurrent Calculi in the Urinary Tract, *Ann. Surg.* 96:133 (July) 1932.

took on a healthy appearance. In these cases an ammoniacal odor is a forewarning that the wound may break down.

Second, Randall applied slightly different measures in cases in which breaking down of the wound had been prevented, but a threat of injury to the wound remained in the form of a persistent pool of alkaline urine. Acidifying drugs given by mouth or topical applications to the orifice of the fistula were not adequate. Consequently, he irrigated the bladder with a 1 per cent solution of phosphoric acid. Such a solution was not irritating, and even a 2 or 3 per cent solution could be used without marked irritation. Following irrigations of the type described, normal acidity of the urine in the bladder returned; thereafter, this acidity could be maintained by administration of acidifying drugs by mouth.

Randall stated that this finding naturally led to the attempt to accomplish the same results in cases of recurrent calculi in the upper part of the urinary tract. As he stated, the stones which form in these cases practically always are phosphatic, and with this in view, he reported 3 cases in which he had irrigated the renal pelvis postoperatively with a solution of phosphoric acid in the hope that by so doing infection with the organisms which have the characteristics described might be avoided. If development of these organisms could be prevented, a means would be secured toward the prevention of recurrent calculi in the upper part of the urinary tract.

Randall experimented on dogs' kidneys by injecting 1, 3 and 5 per cent solutions of phosphoric acid through the ureter from a laparotomy incision. One kidney was removed immediately, and the second one at the end of forty-eight hours. He had not been able to demonstrate, on microscopic study of these kidneys, any evidence of injury to the epithelial lining of the pelvis or to the renal papillae. There was no evidence in these sections of any caustic action from the use of the drug in these strengths. In summarizing, he stated that phosphoric acid, 1 per cent, has a hydrogen ion concentration equivalent to tenth-normal hydrochloric acid or approximately a  $p_H$  of 1.5, and on this bactericidal value is based the statement that phosphoric acid, 1 per cent, is practically isotonic and is approximately equivalent to a gastric acidity of 100. He concluded that the dissolution of small phosphatic calculi, or of fragments left at operation, may be expected because of the recognized action of such strengths of phosphoric acid in vitro and the tolerance to such topical applications in vivo.

Papin<sup>4</sup> analyzed 136 cases of renal lithiasis. The indications for radical and conservative operation are outlined. Nephrectomy was performed on 65 patients, conservative operations on 64, and all types of

4. Papin, E.: Etude sur la chirurgie de la lithiase rénale et en particulier sur les méthodes conservatrices, Arch. d. mal. d reins 6:493 (May) 1932.

intervention were contraindicated in 7 cases. In 5 of 9 cases, death was due to operative shock following the removal of large infected kidneys; death in 1 of the others was due to pulmonary congestion, rupture of an abnormal artery and fistula of the small intestine. Nephrectomy was indicated for the following conditions: hydronephrosis in 17 cases; calculous pyonephrosis in 11; coralliform stones in 16; large stones in 6 and multiple stones in 6; pyelotomy, impossible and nephrectomy dangerous in 2, and atrophic kidney, retrorenal abscess with an infected kidney, pelvic kidney, horseshoe kidney with a fistula, fistula persisting after nephrotomy, rupture of the ureter and rupture of an abnormal renal vein in 1 case each. These indications depended on the integrity of the opposite kidney, which must have good functional capacity without signs of lithiasis, although this last requirement was not absolute. As long as nephrotomy was the conservative operation most often performed, it was rightly regarded as more dangerous than nephrectomy, but today pyelotomy is used much more commonly, and even when nephrotomy is done it is no longer necessary to have recourse to large renal incisions, owing to the use of roentgenography and pyelography. Four of the 64 patients treated conservatively died; 3 of these deaths occurred in the series of 12 cases in which nephrotomy was performed and 1 death occurred following pyelotomy, with supuration of the kidney, which required secondary nephrectomy; this represented 1.9 per cent of the 52 cases in which pyelotomy was carried out. In 1 case hemorrhage from the wound and in 1 case repeated internal hemorrhages occurred eight and fifteen days respectively after operation. Recurrence on the same side was observed in 5 cases, three, five and six years respectively following operation, and recurrence on the opposite side in 1 case after a lapse of ten years. Bilateral calculi occurred in 3 cases, and the intervals between operations on the two sides were four months, ten years and one year, respectively.

The procedures that made this conservative operation possible were: (1) complete roentgenographic exploration, by means of both ascending and descending pyelography; (2) an incision of limited scope; (3) improved methods of suture, and (4) replacement of the kidney by means of nephropexy over pledgets of adipose tissue.

Various types of incision were used. In 10 cases pelvionephrolithotomy was carried out with good results. In several cases, the lower pole of the kidney was freely incised and the incision prolonged, when necessary, over the inferior margin of the large lower calix. In other cases the parenchyma was incised along the oblique fold which forms a continuation of the posterior lip of the hilus; this was done sometimes before and sometimes after the pelvis was opened, and by two different technics: a free incision from outside inward, or passing a blunt Reverdin needle between the posterior surface of the pelvis and the large

lower calix on the one hand, and the wall of the sinus on the other, then through the parenchyma, carrying a silkworm suture which was pulled through the parenchyma. Such an incision seldom bled, and catgut sutures over pledgets of fat gave satisfactory hemostasis.

Small incisions of the pelvis itself do not require sutures, but if pyelonephrectomy requires a large incision, Papin always sutures the pelvis first and then the parenchyma above it.

In many cases in which there were small stones, without much infection, the pelvis was left open and the renal fossa was drained, but in the majority of cases transrenal drainage was established. Fixation of the kidney is important. Papin always replaces the organ in a high position, suspending it hammock-fashion by means of its capsule. Whenever the kidney was genuinely movable, he performed a nephropexy at the upper pole.

[COMPILERS' NOTE.—In general, the material presented by Papin brings out several features of renal lithiasis: 1. Early recognition of the disease is associated with a more conservative operative procedure which may be undertaken with slight risk. 2. In a variable number of cases (from 4 to 20 per cent), depending on the chemical type of the calculus and the nature of the infection, renal lithiasis is recurrent, and prophylactic treatment against recurrence over a period of years must be carefully carried out. 3. The author advocates surgical drainage of the kidney and its fixation in a position to insure adequate physiologic drainage, for these features constitute pertinent factors in restoring the kidney to an uninfected state and to a maximal degree of functional capacity. 4. The selection of cases for nephrectomy or for a conservative operation will depend on surgical judgment in each instance. 5. Papin's estimate of good results followed cases in which conservative incision of the kidney or renal pelvis was undertaken. His criteria for nephrectomy are well founded. Furthermore, they are consistent with the clinical judgment of most urologists, in spite of the present-day well merited emphasis placed by American surgeons on conservative renal operations.]

Woytek<sup>5</sup> stated that "pseudonephrolithiasis" is the term applied by Allemann to that syndrome in which the symptoms are caused by organic inflammatory kinks and strictures in the upper part of the ureter, causing disturbances in function. Such cases simulate closely the cases of true stone, since colic and microscopically observed hematuria are often present. The cause is usually an inflammatory process in the perirenal tissue or the kidney itself. Movable kidneys are associated with only a small number of cases.

5. Woytek, G.: Über "Pseudonephrolithiasis," Beitr. z. klin. Chir. 156:389, 1932.



Woytek has observed 60 such cases since 1924, and has divided them into two groups: that in which the onset is sudden and that in which the onset follows influenza, scarlet fever, diphtheria, puerperal sepsis, otitis media, dental infections, enteritis, salpingitis, prostatitis and seminal vesiculitis. The characteristic findings seem to be a round cell infiltration in the mucosa and musculature. Absolute proof of ureteral stricture or kink is best demonstrated by retrograde ureteropyelograms. Intravenous urography can be of secondary help.

Treatment is chiefly conservative. In cases in which the ureters show irreparable injury, it may be necessary to perform nephrectomy.

*Hydronephrosis.*—Walters<sup>6</sup> stated that conservative procedures, such as resection of the renal pelvis, reimplantation of the ureter or removal of obstructions such as peripelvic connective tissue, are strikingly indicated if hydronephrosis is bilateral, and, if unilateral, when sufficient renal parenchyma remains to justify its preservation. The safest and best procedure is the one which produces adequate and complete relief of the obstruction, with only a minimal disturbance of renal, pelvic or ureteral tissue.

Most cases of hydronephrosis are the result of definite obstructions at the ureteropelvic juncture, which in Walters' experience, have consisted for the most part of: (1) anomalous renal blood vessels, (2) peripelvic connective tissue causing angulation and collapse of the ureter, (3) narrowing of the ureter at the ureteropelvic juncture from sub-epithelial fibrosis and (4) incomplete obstruction of the ureteropelvic juncture owing to lateral insertion of the ureter.

The methods of treatment which were used by Walters in a series of 13 cases and which form the basis of his paper consisted of: (1) division of peripelvic connective tissue which was causing angulation and collapse of the ureter; (2) removal of the ureter from its lateral insertion in the pelvis and its reimplantation in a dependent portion; (3) transplantation of the ureter to a position away from an anomalous renal vessel that is too large to sacrifice, and (4) resection of the renal pelvis, the distended, enlarged pelvis being removed in such a fashion that when resutured the ureter is made to assume a dependent position.

In 5 cases, hydronephrosis was bilateral. Two of the patients successfully underwent bilateral renal pelvic resection, one patient more than three years ago, and the other more than a year ago. Both have been in excellent health since the operation, without evidence of obstruction of the urinary tract. In the other 3 cases, operative procedures have been applied only to the kidney which gave symptoms of obstruc-

6. Walters, Waltman: Resections of the Renal Pelvis and Other Plastic Operations for Hydronephrosis; End-Results in 13 Cases, Surg., Gynec. & Obst. 55:508 (Oct.) 1932.

tion and which displayed the largest degree of hydronephrosis. Equally good results have been obtained in these cases. The remainder of the cases in this series were of unilateral hydronephrosis.

Postoperative complications which are likely to occur are: (1) retention of urine within the renal pelvis, which can be controlled by the temporary use of an indwelling ureteral catheter; (2) pyelonephritis, which has been controlled by intravenous administration of neoparsphenamine and mercurochrome; (3) extravasation of urine about the kidney from the line of anastomosis, and (4) the development of cortical abscesses secondary to pyelonephritis. If the last condition develops, nephrectomy at the earliest possible moment should be performed.

*Tuberculosis.*—De la Peña and de la Peña<sup>7</sup> in a review of 325 cases of renal tuberculosis reported that they have found 22 cases of complete ureteral obstruction (6.7 per cent). All of the patients except 1, from whose opposite kidney considerable evidence of infection with acid-fast bacilli also was obtained, were subjected to nephrectomy, without resulting fatality. During the last six years the authors have observed 2 cases in which autonephrectomy was produced following surgical procedures for different conditions. Nephrectomy was performed in both, without fatality.

E. de la Peña undertook experimental studies on autonephrectomy. In rabbits and female dogs, occlusion of the ureter was produced by means of ligature and endoscopic electrocoagulation respectively. Thirty or more days after the experimental occlusion, nephrectomy proved to have been a very safe procedure. From this experimental study it was inferred that endoscopic electrocoagulation, with a moderate spark and low milliamperage, for the purpose of causing occlusion of the ureter, was a safe procedure. Only one dog died; this death may be attributed to the fact that experiments were being performed to learn the greatest spark intensity that could be used, and consequently the technic was faulty. Peritonitis ensued, and death followed. After these studies the authors had the opportunity to apply the conclusions they had reached in 2 cases of renal tuberculosis. The ureters were occluded by fulguration from two to three weeks prior to nephrectomy; in both cases good results were obtained.

The possible dangers attendant on the production of ureteral obstruction by means of electrocoagulation are lessened by leaving a ureteral catheter in place for a few days. Once the acute signs of congestion produced by the electrocoagulation are past, the catheter may be removed, and contraction of the cicatricial scar will slowly pro-

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7. de la Peña, Alfonso, and de la Peña, Emilio: Artificial Occlusion of the Ureter Previous to Nephrectomy in Early Renal Tuberculosis: Preliminary Report of Experimental and Clinical Study, *J. Urol.* 28:343 (Sept.) 1932.

duce occlusion of the ureter. If electrocoagulation of the intravesical portion of the ureter is insufficient, the flow of urine may prevent its closing. In such a case, two or more treatments by electrocoagulation will bring about closure. If complete occlusion of the ureter from the infected kidney is induced, the bladder and genitalia are protected from infection. Also, the other kidney is protected from infection by reflux from the bladder. The condition of the bladder seems to improve after closure of the ureter. This occlusion is apparently an aid to the development of compensatory hyperfunction of the remaining healthy kidney previous to nephrectomy in cases of unilateral renal tuberculosis. It seems to diminish the risk of death from nephrectomy, and it also seems to be the best treatment for tuberculous cystitis in unilateral renal tuberculosis. Sudden hydronephrosis and pyonephrosis are possible dangers; peritonitis, if the technic is faulty, is a more remote danger.

Lieberthal and von Huth<sup>8</sup> stated that physiologic excretion of bacteria by the kidney does not occur. Some bacteria may pass through the kidney and appear in the renal tubules after severe renal injury, such as rupture of blood vessels, severe epithelial degeneration or glomerulonephritis, has been produced by the organisms and their toxins. The authors stated that bacilli of tuberculosis do not pass through the kidneys, from the blood into the urine, under any circumstances because of the comparatively mild immediate action of that organism on the renal tissues. Bacilli of tuberculosis rarely appear in the renal tubules, and then only as the result of a direct extension of a tuberculous lesion through the wall of Bowman's capsule or the wall of the tubule. They also stated that "true" excretion tuberculosis never occurs in the kidney, and "false" excretion tuberculosis occurs relatively seldom. Tuberculous lesions in the medulla of the kidney are usually hematogenous. Previously induced traumatic, degenerative or inflammatory lesions of the kidney do not make that organ permeable for bacilli of tuberculosis. Tuberculous lesions in the renal parenchyma which do not communicate with the renal pelvis seldom, if ever, give rise to bacilluria.

The kidney has a peculiar immunity to hematogenous infection with bacilli of tuberculosis because of its copious blood supply and the comparatively large caliber of its blood vessels. Bacilli of tuberculosis which are circulating in the blood tend to pass through the circulation of the kidney to lodge in other organs. Infection of the kidney occurs only if local disturbances in the circulation or the presence of the bacilli of tuberculosis in larger masses which cause embolism allows the organism to lodge in the renal tissues. Tuberculous nephritis does not exist.

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8. Lieberthal, Frederick, and von Huth, Theodore: Tuberculous Bacilluria and Excretion Tuberculosis: Experimental Study, Surg., Gynec. & Obst. 55:440 (Oct.) 1932.

Day<sup>9</sup> stated that when a tuberculous lesion has advanced to the renal pelvis or collecting tubules, renal tuberculosis never completely heals because of the handicap of hindered drainage and back pressure owing to tuberculous changes in the ureteral wall; that is to say, aside from other possible reasons, a tuberculous kidney excreting bacilli of tuberculosis cannot heal because an incurably strictured ureter interferes with normal drainage and peristalsis. When complete healing does occur, the tuberculous process is limited to the cortex. Day further stated that until the tuberculous process has extended to a calix or the collecting tubules, pus and bacilli of tuberculosis of renal origin will not be found in the urine, and therefore, up to this time, renal tuberculosis cannot be said to have been "clinically established."

*Ptosis.*—Braasch<sup>10</sup> stated that when nephropexy was so widely employed about twenty years ago, cures were claimed as a result in a variety of complaints and conditions, varying from backache to insanity. In recent years, renal fixation has been revived by the urologist, and many different attitudes exist regarding the surgical treatment of ptosis of the kidney. The two extreme views are that surgical treatment is never indicated, and that in most cases of nephroptosis operation should be performed. Adherents to a third view are of the belief that suspension of the kidney is indicated in selected cases only, but there is considerable difference of opinion as to methods of selection and as to the proportion of patients who should be so treated. The liberal members of the group would include many cases with symptoms referred to the kidney, whether or not there is evidence of pyelectasis or urinary retention on urography. The conservative element does not consider operation advisable unless there is definite urographic evidence of renal obstruction, as well as pain referred to the region of the kidney.

Pyelectasis and renal stasis should be the indications for operation and not the degree of ptosis as shown in the urogram. The importance of correct interpretation of the urogram is evident in the selection of patients for nephropexy. In extreme cases pyelectasis is easily recognizable.

Subjective relief should not be relied on unless a year or more has elapsed since operation. At the end of this time, in most cases, either the symptoms will have returned or other symptoms of a similar nature will have appeared. Urographic studies should be made following nephropexy in order to determine the results accomplished. If renal stasis was caused by nephroptosis, evidence of pyelectasis should be

9. Day, R. V.: Renal Tuberculosis: Why Clinically Established Renal Tuberculosis Never Completely Heals, *California & West. Med.* 37:217 (Oct.) 1932.

10. Braasch, W. F.: Renal Ptosis (Editorial). *Surg., Gynec. & Obst.* 55:247 (Aug.) 1932.

either reduced or entirely eliminated. Clinical examination of a considerable number of patients observed several years after operation by various surgeons for ptosis of the kidney would lead to the conclusion that the proportion of patients who obtain satisfactory relief of symptoms by renal fixation is comparatively small. Renal fixation without regard to any evidence of renal obstruction is not desirable.

*Anomaly.*—McNally<sup>11</sup> reported an additional case of unilateral renal agenesis in which the diagnosis was made clinically by cystoscopy and intravenous pyelography. Nineteen other cases were reported from the literature, bringing the total of reported cases to 466. These 20 cases are in agreement with the previous compilations in regard to the side on which the agenesis occurs most often (the kidney being absent on the left side in 15 cases), the condition of the ureter and the frequency of associated malformations. The importance of recognition of the condition before renal surgery is undertaken, is stressed.

Walters and Priestley<sup>12</sup> declared that in all cases in which an abdominal mass is present, a horseshoe kidney should be considered. They stated that unusual difficulty in freeing either renal pole in the course of surgical procedures on the kidney should arouse suspicion of the presence of fused kidney. Fused kidneys may be the site of any type of pathologic change that is seen in the normally developed kidney, but are more subject to diseases incident to urinary stasis. In most cases, fused kidneys lie median to the position that would be occupied by a normal kidney. Various degrees of dystopia and inclination to one or the other side may occur. Males are more commonly afflicted with horseshoe kidneys than are females. The importance of pyelographic examination before renal operation cannot be overemphasized. Alterations in function of horseshoe kidneys depend on the pathologic change present, except when one kidney suffers arrested development. The portions of the ureters that are near the bladder usually are in normal position. The mortality following operation on 50 patients with horseshoe kidneys seen at the Mayo Clinic was 2 per cent.

[COMPILERS' NOTE.—The diagnosis of horseshoe kidney was verified at operation in 68 cases observed at the Mayo Clinic; subsequent information was obtained concerning 58. Five patients had died. Of the 53 remaining patients, 25 stated that they had no symptoms referable to the genito-urinary tract, and 15 had minor complaints such as slight burning or frequency. This is in contrast to the opinion held by many urologists that these patients, after once having trouble, always retain some symptom of disease referring to the urinary tract.

11. McNally, Andrew: Unilateral Renal Agenesis, *J. Urol.* **28**:289 (Sept.) 1932.

12. Walters, Waltman, and Priestley, J. B.: Horseshoe Kidney: A Review of 68 Surgical Cases, *J. Urol.* **28**:271 (Sept.) 1932.

The morbidity of horseshoe kidney is clearly seen in the relation between its occurrence and the frequency with which it requires surgical intervention. In a collected series of 68,000 postmortem examinations Carlier and Gerard found 80 horseshoe kidneys, or 1 in every 850 subjects. In an earlier paper from the Mayo Clinic in which a ten year period of renal surgery was reviewed, 2,424 operations were performed on the kidney for various conditions; 17 of these were on horseshoe kidneys, or 1 in every 142.

Knowledge of the stages of embryologic development by which the kidneys are fused permits a better understanding of the pathologic conditions which result in later life.]

*Aneurysm.*—Lozzi<sup>13</sup> stated that arteriovenous aneurysm of the renal vessels is extremely rare, but that about 40 cases of aneurysm of the renal artery alone have been reported. In experimental work he produced a permanent arteriovenous fistula, and studied the anatomic and functional changes produced in the kidney. He established anastomosis between a renal artery and vein in twenty-four large dogs, all in good general condition. The operation was done on the right side, because access is easier there and the artery is longer. In only four animals did he succeed, however, in making a fistula which could be regarded as permanent. In some cases that were technically successful, the fistula became obliterated, either through simple occlusion of the communication or through partial or total thrombosis of the lumen of the vessels. This Lozzi attributed to the small caliber of the renal vessels. In order to control hemorrhage and obtain an immediate good result he had found it necessary to choose vessels of relatively small caliber, especially arteries, and this fact contributed greatly toward the formation and deposition of thrombi which occluded the fistula or, more often, the artery or vein in question. The best permanent results were produced when the caliber of the vessels was larger, providing wide communication without too much restriction of the lumen. It was important to make the sutures with extreme delicacy and the finest Carrel needles, so that there should be no laceration or enlargement of the opening made by them.

In every case there was diminution of the peripheral pulse, and sometimes complete obliteration. Changes of rhythm or pulse rate were never observed. On the other hand, the kidney became turgid, with a rapid increase of volume and consistence, which was sometimes of great intensity. In a few cases there was a "thrill" on palpation, with re-enforced systole, above and below the fistula. When the fistula was permanent, there were changes in the caliber and structure of the vein.

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13. Lozzi, Vanazio: *Aneurisma artero-venoso sperimentale dei vasi renali*, Policlinico (sez. chir.) 39:357 (June) 1932.

There was always venous congestion of the renal parenchyma, but saciform or fusiform dilatations of the anastomosis never occurred. In some cases foci of hemorrhagic infarcts occurred, owing to the ease with which small thrombi became formed and detached soon after the fistula was made; in only 4 cases was there a total infarct of the kidney.

Chief among the functional disturbances observed was hematuria of greater or lesser degree, appearing as soon as the kidney began to function and conspicuous during the first two or three days, but persisting in microscopic amount several days longer. As there were never any varices of pelvis or calices, Lozzi thought that the hematuria was always due to diapedesis. Whenever the fistula remained open, albuminuria was abundant; it lasted longer than hematuria, and, like the latter, was to be interpreted as due to congestion and epithelial degeneration, whenever it was not the expression of a hemorrhagic infarct. Cylindruria was present during the first days, the cylinders being hyaline and epithelial at first, and granular later.

All these disturbances indicated the changes undergone by the renal circulation following sudden anastomosis. The concentration of nitrogen in the blood, which in all the animals was about 0.2 mg. in each 100 cc. before operation, rose suddenly on the day following, reaching in some animals from 0.55 to 0.6 mg., and remained high for several days until renal function had improved. On the first two days after operation the vascular disturbance was so great as to stop nearly all function of the kidney. Elimination of intravenously injected sodium indigotindisulphonate U. S. P. (indigo carmine) was delayed, being prolonged sometimes from fifteen to twenty minutes on the side on which operation was performed. But the most exact expression of a change of function was given by the elimination of phenolsulphonphthalein. Although this was not delayed, elimination of the drug was deficient, the amount eliminated in the first hour being in some cases scarcely from 10 to 15 per cent. Ten cases in which the fistula became obliterated were of interest because it could be observed that the functional deficit of the kidney on operation was exactly proportional to the degree of arterial stenosis left by the operation.

*Resection.*—Stone<sup>14</sup> stated that heminephrectomy is indicated in the presence of nonmalignant changes when the disease is limited to a single section of a double kidney, and there is a sufficient secretory area in the other segment to make conservation worth while. When an embryonic cleavage plane exists between the segments, it is not necessary to compress the vessels to the segment to be left or to close the exposed surface of the remaining kidney. Stone added that it is wise to expose the entire blood supply of the double organ before resection and to suspend the remaining segment.

14. Stone, Eric: Heminephrectomy, *J. Urol.* 28:301 (Sept.) 1932.

No deaths were reported in the cases reviewed by Stone. In 3 cases the remaining segments had to be removed later. In 22 of 30 cases in which heminephrectomy was performed, the symptoms which led to the operation were relieved. In 2 cases a urinary sinus persisted. Both operations were performed by Rumpell. The first of these operations was stated to be the first heminephrectomy ever performed, and it is probable that a calix was entered and the condition was not recognized; in the other case the ureter to the sound segments was accidentally destroyed, and the ureter to the diseased segment was anastomosed to the normal pelvis.

*Denervation.*—Lozzi<sup>15</sup> published follow-up data on a series of 20 patients on whom he performed renal decapsulation, and reported the late results of the procedure, which were almost uniformly good.

The kidney is innervated by a special plexus formed by fifty-six small trunks which anastomose; these run particularly on the posterior surface of the vascular peduncle, and are more or less adherent to the adventitia, thus making a large meshlike reticulum around the vessels. A second network, more delicate and fine, visible only through the microscope, forms part of the adventitia of the artery, and receives small anastomosing branches from larger superficial trunks. All these nerve fibers, joined at the renal hilus, penetrate in part into the organ, while others, corresponding to the internal aspect of the fibrous capsule, are distributed centripetally, at various intervals, in the cortical substance. These nerves, if interrupted, regenerate with marked promptitude, so that by the end of forty-five months they are completely restored.

The function of the renal plexus is to exert a lively vasomotor action on the arterial circulation of the organ. Renal decapsulation would cause interruption of all these fibers which make connection with the fibrous capsule, and would thus result in partial denervation of the kidney. A thorough search of the literature on the subject does not confirm Edebohl's view that the good effects of renal decapsulation are attributable to the development of collateral, arterial and venous circulation. If this were the case, the good effects would be observed only after the lapse of a certain period of time, whereas, on the contrary, the satisfactory results appear suddenly, immediately after removal of the capsule. Lozzi attributed them to the beneficial nervous influence exerted on the vascular system. In addition, decapsulation also concerns sensory fibers, as is shown by the large number of cases of nephralgia in which cure is effected. Not only does it produce no injurious disturbances either in the parenchyma or in function, but it

15. Lozzi, Vananzio: Risultati lontani della decapsulazione ed enervazione renale, Policlinico (sez. chir.) 39:84 (Feb.) 1932.



even, through improved circulation, promotes a better state of nutrition and therefore of renal function. As soon as decapsulation has been performed, the kidney increases in size and assumes a more arterial color, as the result of vasodilatation, especially venous. This vasodilatation must be explained as the effect of a vasomotor influence from a nerve lesion. This view is supported by Valdon's experiments, in which vasodilatation was obtained only in the decapsulated portions.

Clinically, the hypothesis of vascular action is supported by numerous arguments, such as its immediate occurrence, explainable only by the cessation of a nervous action on the vessels, and the immediate cessation of pain in acute nephralgia, which could be the result only of destruction of the capsular sensory terminations of vascular action.

A review of the literature reveals that the results were good in the majority of cases on record. Lozzi's own 20 cases included 3 of anuria, 8 of painful hematuric nephritis, 2 of adhesive perinephritis and 2 of pyelonephritis. In 19 cases there was either cessation of the syndrome or marked improvement. The late results can also be regarded as satisfactory, since clinical cure persists in about 75 per cent. In 1 case of anuria only did death occur after operation, owing to the presence of a small calculus in the ureter of a solitary kidney which had been overlooked in the roentgenogram. Two deaths resulted from uremia one and two years respectively after decapsulation. Permanent clinical cure had been obtained in the remainder of cases. Late functional tests were perfect, after decapsulation and enervation. The rapid reestablishment of diuresis after anuria and the disappearance of the clinical syndrome in cases of painful hematuric nephritis must be regarded as due solely to a vasomotor effect exerted on the vascular system of the renal parenchyma which, through improved conditions of circulation, necessarily underwent improvement both anatomic and functional. Even in cases in which decapsulation was applied without precise indications, it produced immediate and lasting satisfactory results.

*Perinephritic Abscess.*—Crenshaw<sup>16</sup> reported 2 cases, which serve as reminders of the fact that the occurrence of a perinephritic abscess rupturing into a bronchus is rare. He reported that this complication does occur and should be thought of when a perinephritic abscess is accompanied by a cough, particularly when the patient is in the recumbent position, or by excessive sputum and elevation of the diaphragm, and conversely, that it should be considered when pulmonary symptoms are accompanied by or preceded by findings suggestive of renal disease. He stated that early diagnosis and early drainage of the perinephritic abscess would greatly reduce the pulmonary injury.

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16. Crenshaw, J. L.: Pyonephrosis with Nephrobronchial Fistula, *J. Urol.* 28: 427 (Oct.) 1932.

*Infection.*—Hyman and Edelman<sup>17</sup> stated that invasion of the blood stream in diseases of the urinary tract is not uncommon. Two types of infection are generally recognized: bacteremia, which is generally transitory and is attended by little if any mortality, and septicemia, which is grave and is attended by high mortality. The majority of infections of the blood stream observed by the authors were due to some form of urethral instrumentation or originated after operation. Forty-five of the 64 cases studied were due to bacillary infections, with a mortality of 20 per cent; 19 were due to coccal infections, and 68.4 per cent of the patients died. The main factor in treatment is adequate care of the primary focus of infection.

*Tumors of the Renal Pelvis.*—MacKenzie and Ratner<sup>18</sup> stated that the types of tumors that arise in the renal pelvis are similar to those that occur in the bladder. Most of them are derived from mesodermal tissue. About from 40 to 50 per cent of all tumors of the renal pelvis are papillomas. They usually are multiple and appear as villous or wartlike growths similar to those found in the bladder. Often there is one large tumor, with several smaller tumors surrounding it. Frequently these growths are associated with salty incrustations and even with definite calculi.

Papillary epithelioma comprises about from 20 to 30 per cent of the growths of the renal pelvis. These tumors are also wartlike, but appear more compact and involve a greater area than the simple papillomas. In the early stages of the growth there is definite evidence of involvement of the submucosa, and later the renal parenchyma is encroached on. In advanced cases there is usually distention of the renal pelvis, and multiple cysts are present in the cortex of the kidney. These tumors are also extremely vascular and bleed easily.

Squamous cell carcinoma comprises a small group, but a fair number of cases have been reported in the literature. The importance of previous infection as a causative agent should be emphasized. Leukoplakia with calculi also seems to play a part, as several of the cases described have been associated with these conditions. The lesions grow rapidly and involve the renal parenchyma and the surrounding tissues.

The most outstanding symptom in tumors of the renal pelvis is hematuria. Pain is not a constant symptom. At times a patient complains of a dull ache in one or the other loin. Occasionally there is typical renal or ureteral colic. This is due to the passage of a small transplant or blood clot down the ureter. Severe pain may also result

17. Hyman, A., and Edelman, L.: Medical and Surgical Aspects of Hemogenous Infections in Urology, *J. Urol.* 28:173 (Aug.) 1932.

18. MacKenzie, D. W., and Ratner, Max: Tumors of the Renal Pelvis: A Review of the Literature and Report of a Case, *J. Urol.* 28:405 (Oct.) 1932.

when obstruction occurs at the ureteropelvic angle, causing hydronephrosis or hematonephrosis.

In a large number of cases a mass cannot be palpated. This is particularly true when the growth is small or when it is spreading toward the upper pole of the kidney. The most common cause of a palpable tumor is probably associated hydronephrosis or hematonephrosis due to some form of obstruction.

MacKenzie and Ratner further stated that although simple papilloma of the renal pelvis is benign, clinically it is potentially malignant. It has the property of forming transplants in the ureter and bladder and even in the opposite ureter. The most malignant papilloma gives a better prognosis than other malignant growths of the renal pelvis. The most malignant tumor of the renal pelvis is the squamous cell carcinoma. It metastasizes early and extensively. The results are poor even when treatment is given early.

MacKenzie and Ratner stated in conclusion that on account of the tendency of tumors of the renal pelvis to extend down the ureter and even to the bladder, the treatment of choice today is nephrectomy and complete ureterectomy.

*Pararenal Tumors.*—Didier and Leibovici<sup>19</sup> reported 2 cases of paranephritic fibrolipomas; one tumor weighed 3.75 Kg. and the other 10 Kg. Although these tumors are very large, growths have been observed that weighed as much as from 20 to 30 Kg. They occur more frequently among women, and have occasionally been diagnosed as ovarian cysts. Histologically, the tumors are usually fibrolipomas; rarely do they become malignant; nevertheless they have a tendency to recur locally, so that even if operated on, they usually cause death from cachexia in a few years, the patient becoming emaciated as the tumor grows larger. The great size of these tumors, the plane of cleavage sometimes to be found between their several lobes, and their tendency to put forth distant prolongations make it impossible to determine whether the growth has been entirely removed. Rarely has the diagnosis been made clinically. At present it would appear that modern means of diagnosis are at hand which, if they do not permit an absolutely exact diagnosis, at least eliminate certain current diagnoses, such as ovarian cyst. Use of the barium sulphate enema would show the exact situation of the tumor relative to the colon, which these growths flatten and generally empty of gas.

The condition of the kidney is of diagnostic aid. Usually the kidney is destroyed either by the tumor or at the time of operation (removal). Consequently, the function of the opposite kidney should be determined before operation. More than half the operations for

19. Didier, Robert, and Leibovici, Raymond: Deux volumineux fibro-lipomes paranéphrétiques, Bull. et mém. Soc. nat. de chir. 58:1068 (July 16) 1932.

pararenal tumors have ended with total extirpation of the kidney, the sacrifice of which has often been unnecessary. In many cases, the kidney is not invaded by the growth and can be separated from it and conserved; renal adhesions are usually only to the capsule. If the tumor is at points adherent to the parenchyma, it is easy to detach a small section of the renal tissue with the tumor.

The first step in the operation should be to find the ureter at the lower pole of the kidney. Whether the operation is performed by the transperitoneal route, as is occasionally done, or by the lateral subperitoneal route, the method favored by Didier and Leibovici, it should always be possible to find and isolate the upper part of the ureter. Conservation of the kidney, in fact, usually depends on the renal pedicle. If the pedicle can be isolated, conservation should be attempted, unless the kidney appears diseased. If, however, the renal vessels penetrate within the tumor, and if to conserve them one must risk performing an incomplete operation, the kidney must be sacrificed.

*Differentiation of Right-Sided Renal Disease from Appendicitis.*—Salleras<sup>20</sup> asserted that there is an extraordinary amount of confusion in the diagnosis of right-sided nephrosis and appendicitis. The type of pain and its situation are of no value for diagnosis, as they may be exactly the same. In painful renal diseases, however, there are almost never lacking such vesical reflex symptoms as pollakiuria, dysuria and oliguria which may end as the pain declines with marked polyuria and with the elimination of several liters of urine, according to the length of the attack. In appendicitis, on the contrary, nothing like this occurs. In both conditions, the symptoms are the same. The ureteral catheter will reveal a stone if it is in the urinary tract. Examination of urine from the ureteral catheter frequently reveals infections which cause pain simulating appendicitis.

The pyelogram, however, gives the most accurate differential data. In some cases it discloses slight uronephrosis caused by an anomalous vessel. A pyelogram likewise shows up stones which may be permeable to roentgen rays, thus preventing confusion. After the injection of pyelographic mediums repeated roentgenograms, taken at intervals of ten minutes, not only help in making the diagnosis, but also show the state of contractility of the renal pelvis.

The occasional renal, vesical or perinephritic complications secondary to acute appendicitis make pyelography doubly important. Salleras described cases in which the appendix was low in Douglas' culdesac and caused reflex vesical symptoms, cases in which retrocecal appendix was complicated by perirenal abscesses and cases in which a perforated

20. Salleras, J.: Uronefrosis derecha y apendicitis, Rev. Asoc. méd. argent. 46:478 (June) 1932.

appendix was in contact with the renal pelvis. He also observed cases of hematuria secondary to acute appendicitis, in which appendectomy caused complete cure, a fact that can be explained by the action of toxins or micro-organisms which reach the kidney by way of the blood stream.

[COMPILERS' NOTE.—It seems proper to emphasize that in dealing with doubtful cases of so-called chronic appendicitis or pain on the right side of the abdomen, it should be a rule that operation should not be performed until changes in the right kidney have been ruled out by either an intravenous urogram or a complete urologic examination.]

*Anomalies.*—Williams<sup>21</sup> reported the discovery at necropsy of complete bilateral duplication of the ureters of a girl aged 18 years, who was five months pregnant. The four ureteral orifices were observed, and each of the four ureters allowed the passage of a probe. An attempt to catheterize one of the right ureters during cystoscopic examination met with obstruction after the catheter had entered about 12 cm. This proved to be due to a diminution in the caliber of the ureter and not to a mucosal fold or calculus, as suspected. This ureter was of varied caliber in several places, whereas its double was almost uniform throughout and of greater diameter, and would have received a catheter without difficulty.

*Stone.*—Goldman<sup>22</sup> reported that the specimen which he presented is one of the largest ureteral calculi described in any of the literature available to him, and that the patient is the youngest reported to have been operated on for the removal of a stone of that character and size. The stone was extracted entire from the ureter, and a small calculus adjacent was secured after some efforts with finger and forceps. Recovery was uneventful; a sinus did not develop, and the wound was entirely healed in fourteen days. The boy had gained more than 30 pounds (13.6 Kg) seven months after operation; the urine was clear, but contained a few pus cells. He had no urinary symptoms, and continued to gain in strength.

The stone weighed 125 Gm. on removal, and measured approximately 18 cm. in length and 9 cm. in circumference. Goldman also gave a good review of the literature on large ureteral stones.

Mathé<sup>23</sup> stated that the diagnosis of stone in the ureter can be accurately made with the perfected methods of ureteral investigation and roentgenologic study now in use. The majority of stones in the ureter

21. Williams, Pauline: Complete Bilateral Duplication of the Ureters, *J. Urol.* **28**:279 (Sept.) 1932.

22. Goldman, Max: Mammoth Ureteral Calculus: Report of a Case, *J. Urol.* **28**:371 (Sept.) 1932.

23. Mathé, C. P.: The Diagnosis and Present-Day Treatment of Ureteral Stone, *J. Urol.* **28**:133 (Aug.) 1932.

can be made to pass by dilation exceeding the diameter of the calculus and by incision of any accompanying congenital stricture of the meatus. The indiscriminate use of metal instruments to induce the calculus to pass may often result in injury to the ureter that exceeds the occasional immediate successful removal of the stone. The persistent use of cystoscopic manipulations to relieve impacted calculi lodged in a localized dilated portion or diverticulum of the ureter is not advisable and subjects the kidney to irreparable injury. Uterolithotomy should be performed for impacted calculi, for calculi that show no tendency to descend, for calculi in the solitary or bifid ureter and in cases in which it is impossible to make repeated cystoscopic examinations.

*Pyo-Ureter.*—Molina<sup>24</sup> reported 2 cases in which, at nephrectomy, the infected stump of the ureter was not removed with the kidney. Cases of renal tuberculosis often occur, in which the whole or part of a ureter in a pathologic condition is not removed with the kidney. Suppuration and infection continue, until sometimes it is necessary to remove the ureter at a later operation. Although nephro-ureterectomy is now an established principle in cases of renal tuberculosis in which the infection extends to the ureter, its significance has not been sufficiently recognized in other cases in which nephrectomy is performed. At times the ureteral stump becomes a hard, sclerotic cord after the passage of a certain period, but this is not always the case.

In the first case reported, the kidney had been removed because a large stone was present, but a calculus in the lower part of the ureter had been overlooked. Pyo-ureter developed, which at first discharged its content into the bladder; later the stone obstructed the ureteral orifice, and because of back-pressure and infection, an abscess formed in the wall of the lumbar region. In the second case the patient complained of intense pain; this was caused by three calculi in the lower part of the ureter.

In accordance with Jeck's conclusions, Molina stated his belief that pyo-ureter is caused by obstruction of the ureter and by lesions of its innervation, resulting in absence of peristalsis and loss of tonus. In most cases the principal etiologic factor is calculus in the ureter. This condition is best prevented by appropriate treatment of the ureter and its content at the time that nephrectomy is performed. Although in some cases methods such as fulguration and irrigation are successful, ureterectomy, especially total ureterectomy, is indicated in the majority of cases. If this is not done and an abscess of the wall with a post-operative secondary fistula develops, it is necessary to reopen the wound and to resect all the infected perirenal tissue.

24. Molina, L. F. R.: Dos casos de pio-ureter, *Ann. de cir. (Havana)* 4:457 (July) 1932.

[COMPILERS' NOTE.—It is obvious that when the ureter is involved in the pathologic process of the kidney, or vice versa, and the condition is clearly recognized before operation, the proper treatment is ureteronephrectomy. Gutierrez<sup>25</sup> recently reviewed the indications for ureterectomy. He considered the value and convenience of making two separate incisions in order to accomplish total removal of the kidney and ureter in one piece without opening. To obviate failure in nephrectomy, a pyelo-ureterogram should always be taken before operation. When this is not possible by either the retrograde or the intravenous method of pyelography, the urologist should be prepared to perform complete nephro-ureterectomy when indicated.]

*Rupture.*—Wesson<sup>26</sup> stated that the wall of a normal ureter cannot be punctured by a catheter, and it is doubtful if a diseased ureter can be perforated unless a deep ulcer is present. By means of necrosis caused by pressure, stones produce leaks or openings through which they penetrate, and the resultant perinephritic abscess may drain into the ureter or bowel or to the external surface.

Perforation of the ureter when it is catheterized through the cystoscope is impossible, for the catheter buckles in the bladder if the point meets with resistance. In an experimental study of specimens removed at necropsy, the bladders were finally opened and the mouths of the ureters held with artery forceps so that the maximal amount of pressure could be exerted by the tip of the catheter. The most severe test was to tie a ureter in a knot, and in no case was perforation produced by a catheter.

*Fistula.*—Hunner and Everett<sup>27</sup> reported a case of urinary ascites resulting from a traumatic fistula of the right ureter following supravaginal hysterectomy for fibroid tumors. Although the urinary ascites was present for more than a week the patient was not severely ill, and a satisfactory cure was obtained by severing the ureter at the site of the fistula and reimplanting it into the bladder. The patient has remained well since.

Hunner and Everett reported a second case, which, although different from the first both in etiology and in outcome, is reported as additional evidence that the peritoneal cavity can tolerate large quantities of urine over a considerable time without the patient experiencing any severe reaction. This case was one of carcinoma of the cervix; the patient had received radium and roentgen therapy, and later a vesico-

25. Gutierrez, Robert: Indications and Technic of Combined Ureteronephrectomy, *Ann. Surg.* **93**:511 (Feb.) 1931.

26. Wesson, M. B.: Rupture of Ureter: A Medico-Legal Problem; Report of Cases, *California & West. Med.* **37**:296 (Nov.) 1932.

27. Hunner, G. L., and Everett, H. S.: Uretero-Peritoneal Fistula with Urinary Ascites, *J. Urol.* **28**:333 (Sept.) 1932.

vaginal fistula and a ureteroperitoneal fistula developed. The ureters were transplanted to the colon; the patient died of uremia. Necropsy revealed generalized chemical peritonitis.

This case also calls attention, in a striking manner, to some of the late effects on the deeper tissues of the massive irradiation sometimes necessary for overcoming malignant growths. However, Hunner and Everett have previously reported on the rapidly increasing group of cases in which, following pelvic irradiation, ureteral and periureteral changes develop that lead to urinary stasis and renal injury. These investigators expressed the belief that in the future all patients who have received heavy irradiation of the pelvic organs should be advised to report at intervals of six months for careful investigation of the ureters to insure that the function of these organs is not being seriously jeopardized.

*Implantation.*—Green-Armytage<sup>28</sup> stated that since Coffey's improvements in the technic of ureterorectoneostomy which have extended the indications for the operation, a number of modifications have been reported for the purpose of simplifying this procedure. Green-Armytage reported 8 cases of bilateral simultaneous transplantation of the ureters in which he used a straight metal tube to convey the ureteral catheters through the anus. Thereby he eliminated the time-consuming preliminary irrigation of the bowel through a cannula and rectal packing through a sigmoidoscope, which was the technic used by Coffey. Green-Armytage used a metal urethral catheter the curved end of which was cut off and a straight conical screw bulb substituted. This was passed through the stab wound in the mucosa at the distal end of the incision, through the muscularis and, with the aid of a Kelly cystoscope, out of the anus. The catheter, which had been fixed in the ureter by a single ligature of 000 catgut, was passed through this metal tube, which was then removed and prepared for use in anastomosis of the other ureter.

Green-Armytage did not use the tight ligature of the ureter to the ureteral catheter, by which the ureter is cut through in several days, nor did he use the pack which Coffey thinks is so essential in all cases of bilateral simultaneous anastomosis. He reported 10 cases of severe vesicovaginal fistula, in 2 of which bilateral simultaneous anastomosis was made without using the tube technic; in the other 8 cases, his modification of the tube technic was employed.

Burman<sup>29</sup> reported the case of a patient with a vesicovaginal fistula whose right ureter was implanted into the cecum through the stump of

28. Green-Armytage, V. B.: Implantation of the Ureters for Inoperable Vesico-Vaginal Fistula and Ectopia Vesicae: A New Technique, *Brit. J. Surg.* 20:130 (July) 1932.

29. Burman, C. E. L.: A Case of Transplantation of the Right Ureter into the Caecum and of the Left into the Sigmoid Five Years Afterwards, *Brit. J. Surg.* 20:44 (July) 1932.



the appendix. Five years later the left ureter was transplanted into the sigmoid. Intravenous urograms one month after the second operation showed advanced hydronephrosis on the right side and early hydronephrosis on the left side. The patient died from an undetermined cause two months after the second operation.

[COMPILERS' NOTE.—Coffey's<sup>30</sup> latest contribution to the technic of ureterorectoneostomy is the transfixion suture method or technic 3. The same incision is made in the intestine down to the mucosa, which, however, is not opened. The end of the freed ureter is ligated and brought into the interlamellar space outside the intestinal mucosa by an anchor stitch which fastens the end of the ureter in the angle of the caudal end of the incomplete intestinal incision. A transfixion suture of silk or linen is then taken through the ureter and the intestinal mucosa and is tied tightly. It cuts through in from twenty-four to forty-eight hours and completes the anastomosis. Coffey reported 3 cases in which the operation was performed by this method, in one instance by Brunn and in the others by himself. Coffey's technic was employed by one of the compilers in a case of exstrophy of the bladder, and the absence of postoperative reaction as compared to that which follows when other methods are employed was impressive. Intravenous urography three months postoperatively demonstrated absence of pyelocaliectasis or ureteral dilatation. Technic 3 is much simpler than technic 2 or even technic 1, and is an outstanding contribution to methods of diverting the urine to the bowel.]

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30. Coffey, R. C.: Transplantation of Ureters into Large Intestine by Submucous Implantation: Clinical Application of Technic, *J. A. M. A.* **99**:1320 (Oct. 15) 1932.

(To be continued)

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## MALIGNANT TUMORS OF THE MALE BREAST

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Diseases, or specifically malignant neoplasms, of the male breast, are sufficiently common to be of interest to the practitioner of medicine, of significance to his patients and of importance to the surgeon. To many members of the medical profession, as well as to the layman, cancer of the male breast erroneously appears rather as a myth, and therefore inconsequential.

The literature on cancer of the male breast is interesting and instructive, but there is no intent to cover it in detail in this article. From it, however, critical and pertinent remarks gleaned here and there will be used to substantiate my findings and to emphasize certain points. Many of the almost 200 articles that I have read on the subject deal with case reports, statistical compilations or clinical studies, and not with laboratory, or more specifically histologic, observations, the criteria around which the discussion in this paper will be constructed.

Of the reasons for making this report, the following are worthy of enumeration:

1. To record a study in which the histopathologic diagnosis has been the critical and conclusive feature in a group of 60 malignant new growths found in the male breast, and encountered in the laboratory diagnosis of 9,279 mammary glands.

2. To obtain accurate information as to prevalence and types of malignant growths of this male organ for the guidance of the members of the profession, and as a source for comparison in future studies.

3. To demonstrate that much of the past statistical material varies widely from facts that are found today under an entirely different set of conditions than existed in 1890 or even in 1910.

4. To add material of a practical character to the summed up knowledge of the malignant conditions of the breast.

5. To direct the attention of the medical profession to the adult male breast as an organ that is the potential site for malignant new growths, and that therefore should be examined as a routine.

In 1930, Neal and Simpson<sup>1</sup> classified and recorded the diseases found in a group of 152 male breasts. The present paper includes data

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From the Department of Pathology, University of Missouri School of Medicine.

1. Neal, M. Pinson, and Simpson, Burton T.: *Diseases of the Male Breast*. J. Missouri M. A. 27:565, 1930.

TABLE I.—

Series Number	Identification Number	Surgeon	Date of Operation	Case Designation	Marital Status	Age at Operation	Breast Involved	Duration Before Operation	History of Injury	Clinical Diagnosis
1	467	Parmenter	Oct. 1905	G. R.	—	—	—	—	—	—
2	1321	Wright	Jan. 1911	F. R.	—	—	—	—	—	—
3	1936	Porter	Oct. 1911	F. K.	—	—	—	—	—	—
4	2146	Clinton	Jan. 1915	H. A. V.	S	51	—	—	—	—
5	2781	Clinton	June 1915	Ha.	M	50	—	—	—	—
6	2865	Truesdale	July 1915	—	M	58	R	—	14 yrs. ago	Carcinoma
7	2965	Mulenny	Aug. 1915	—	—	—	—	—	—	—
8	3111	Redmond	Sept. 1915	Hu. R. E. A.	—	51	—	18 mos.	—	Carcinoma
9	4391	Cottis	May 1916	O. J.	M	53	R	—	—	?
10	4847	La Porte	July 1916	D.	M	58	—	1 year	—	Carcinoma
11	5220	Jameson	Oct. 1916	C. E. W.	M	72	—	1½ years	—	Cancer
12	5199	Loop	Nov. 1916	D. T.	M	60	—	6 weeks	—	Epithelioma
13	6225	Lenz	Mar. 1917	A. A.	M	54	—	—	—	Carcinoma
14	6329	Clinton	Mar. 1917	J. W. C.	M	57	—	2 years	—	Fibroma
15	7928	O'Connor	Dec. 1917	Z. v. B.	M	67	—	3 years	—	Carcinoma
16	8325	Douglas	Feb. 1918	W. J. G.	M	50	—	—	—	Carcinoma
17	8358	Sullivan	Feb. 1918	W. G.	M	71	L	2 years	—	Carcinoma
18	8753	Costello	Apr. 1918	Sch.	M	40	—	3-4 weeks	—	?
19	9607	Kittlinger	Aug. 1918	E. S.	M	59	—	3 years	—	Fibroma
20	15053	Smith	Oct. 1919	A. Am.	S	51	L	6 mos.	—	Carcinoma
21	15639	McGuire	Dec. 1919	C. G.	M	64	L	1 year	—	Carcinoma
22	20317W	Schroeder	June 1920	O. V. N.	M	47	—	6 mos.	—	Chronic mastitis
23	15889	Schreiner	July 1920	J. D.	M	55	L	2 mos.	—	Tumor
24	15928	Schreiner	July 1920	J. D.	M	59	R	1 year	—	Epithelioma
25	16880	Smith	Oct. 1920	W. W.	M	60	—	—	—	—
26	18796	Drumm	Feb. 1921	J. O'C.	S	59	—	3 years	—	Carcinoma
27	21502	Manly	Aug. 1921	C. H.	S	57	L	—	—	?
28	27347	Hovey	Sept. 1922	C. McA.	M	48	R	—	—	Sarcoma
29	29641	Prince	Mar. 1923	A. T.	M	43	—	1½ years	—	Carcinoma
30	30732	Jameson	Mar. 1923	B. V.	M	50	—	Months	—	Carcinoma
31	31487	Kress	June 1923	McG.	M	48	L	—	—	Fibrosarcoma
32	33219	Hulbert	Sept. 1923	—	M	50	L	8 mos.	Years ago	Nervous carcinoma
33	39215	Cooperhall	Sept. 1924	DeF. L.	M	53	L	1 year	Repeated	?
34	26642M	Hafner	Dec. 1924	L. K.	M	54	R	1 year	—	Tumor
35	41442	Bush	Jan. 1925	Arn.	M	62	—	Months	Year ago	Cancer
36	25-20M	Nifong	Jan. 1925	D. D. M.	M	69	R	—	—	Carcinoma
37	44106	VanLengen	June 1925	J. W.	M	52	L	—	—	Carcinoma
38	47200	O'Meara	Nov. 1925	Bro. R.	S	58	—	Years	Repeated	Carcinoma
39	51431	Redfield	June 1926	E. M.	W	67	L	1 year	—	Carcinoma
40	55414	Schreiner	Nov. 1926	S. T.	M	50	—	—	—	Carcinoma
41	27830M	Rowland	Apr. 1927	C. W.	S	28	R	—	—	?
42	58372	Stewart	Apr. 1927	S. B. C.	S	52	—	—	—	Cancer
43	60737	Schreiner	July 1927	S.	M	54	L	4 years	—	Carcinoma
44	60901	Fisher	July 1927	R. W.	M	58	L	—	—	Carcinoma
45	68376	McLeod	May 1928	A. L.	—	41	—	—	—	?
46	71203	Turner	Aug. 1928	P. R.	M	—	—	—	—	?
47	73690	Smith	Nov. 1928	L. D.	M	49	R	—	—	Growth
48	73812	Quinn	Dec. 1928	Wm. W.	M	72	L	—	—	—
49	76747	Quinn	Mar. 1929	H. M.	M	67	R	—	—	Carcinoma
50	84686	Carpenter	Nov. 1929	W. J.	M	74	R	—	—	Syphilis (?)
51	88703	Stuart	Apr. 1930	T. E.	M	50	L	—	—	—
52	90476	Kane	May 1930	F. L. S.	M	58	R	2 years	—	Malignancy
53	91540	Kelly	June 1930	J. M.	M	69	—	1 year	—	—
54	93234	Johnson	Aug. 1930	A. E. B.	—	70	—	Months	—	Malignancy
55	97017	Reld	Dec. 1930	T. B.	M	51	—	—	—	Malignancy
56	97225	Robinson	Dec. 1930	S. M.	M	69	—	5 weeks	—	Tumor
57	98579	McGarvey	Jan. 1931	J. J. J.	M	62	L	—	—	Carcinoma
58	99936	Chandler	Feb. 1931	S. G.	S	22	—	—	—	Carcinoma
59	102169	Kress	May 1931	J. T.	M	70	L	—	—	—
60	103408	Lutcher	June 1931	G. C.	M	55	R	—	—	Sarcoma

# Details of Cases

Histopathologic Diagnosis	Degree of Malignancy	Mitotic Cells	Lymphocytic Infiltration	Stroma	Metastasis	Comment
Medullary carcinoma	High	Few	Scant	Scant	—	
Carcinoma simplex	Moderate	Rare	Abundant	Moderate	—	
Fibrosarcoma	High	Many	None	None	Axilla	Size of orange; extends into axilla
Scirrhus carcinoma	Moderate	Few	Few	Abundant	—	Began at margin of nipple
Medullary carcinoma	Moderate	Few	Moderate	Moderate	Axilla	Death after 2 years; metastasis to lung and liver
Fibrosarcoma	High	Many	None	None	—	Histologic invasion of muscle
Fibrosarcoma	Moderate	Few	None	None	—	
Medullary carcinoma	High	Many	Small amt.	Scant	Axilla	Rapid growth; death 7 months after operation
Medullary carcinoma	Moderate	Many	Scant	Moderate	Axilla	Ulceration of covering skin; 1½ inch mass below nipple
Duct cell carcinoma	Low	Rare	Scant	Much	—	Bloody discharge from nipple; living 6 years later
Duct cell carcinoma	Moderate	Few	Scant	Scant	Axilla	Death after 2 years; metastasis to lung and liver
Leiomyosarcoma	Moderate	Few	None	Scant	—	Oval, slow growing, capillaries dilated; roentgen therapy for 2 years before operation
Scirrhus carcinoma	Low	Rare	Many	Much	Retropectoral nodes	Death 5 years later; no evidence of carcinoma
Adenocarcinoma	Moderate	None	Few	Moderate	Axilla	Extensive growth and invading axilla
Carcinoma simplex	Moderate	Rare	Many	Moderate	—	Slow growing; 8 by 16 cm. oval tumor
Duct cell carcinoma	Moderate	Few	Few	Moderate	None	Living 5 years later
Basal cell carcinoma	Low	None	None	Scant	None	Painful for 2 months
Medullary carcinoma	High	Many	Many	Scant	None	Axillary node-hyperplasia only
Carcinoma simplex	Moderate	Few	Many	Moderate	—	No recurrence end of 4 years
Medullary carcinoma	Moderate	Rare	Scant	Moderate	—	No recurrence end of 2 years
Adenocarcinoma	Low	Rare	Scant	Moderate	—	No recurrence end of 4 years
Liposarcoma	High	Few	None	Scant	—	Size of orange; lemon yellow color
Medullary carcinoma	High	Few	Scant	Scant	Axilla and skin	Clinical diagnosis, epithelioma of nipple; death 6 months later; many metastases
Medullary carcinoma	High	Few	Few	Scant	Skin; right arm	Death after 6 months; many metastases
Duct cell carcinoma	Moderate	Few	Scant	Scant	Axilla	Death soon after operation
Chondromyxosarcoma	Moderate	Few	None	None	—	Fixed; fast growth for 3 or 4 months; size of ham, lobulated; gelatinous contents
Melanocarcinoma	High	Many	Few	Scant	Axilla	Marked pigmentation and in node
Scirrhus carcinoma	Low	None	Abundant	Marked	None	Nipple over center and exudes serum
Medullary carcinoma	High	Few	Small amt.	Scant	Axilla	Breast removed 5 months ago; invades muscle; death in few months; wide metastases
Fibrosarcoma	Moderate	Few	None	None	None	9 by 8 by 8 cm. tumor; no recurrence end of 9 months
Nevus cell carcinoma	Moderate	None	Scant	Scant	—	Stroma, very vascular; death in 6 months; carcinoma
Carcinoma simplex	Moderate	Few	Abundant	Moderate	—	Serous discharge from nipple; histologic invasion of muscle
Medullary carcinoma	High	Many	Scant	Scant	Axilla	Tumor size of egg
Duct cell carcinoma	Moderate	Many	Moderate	Scant	—	Followed fall against farm implement
Scirrhus carcinoma	Low	None	Scant	Abundant	Skin	Metastatic nodule near breast
Medullary carcinoma	Moderate	Few	Scant	Scant	None	Death 6 years later; see case report
Medullary carcinoma	High	Many	Many	Scant	—	Organ twice normal size
Basal cell carcinoma	Low	None	None	Scant	—	
Scirrhus carcinoma	Moderate	Few	Myriads	Moderate	Axilla	Tumor size of silver dollar and irregular
Nevus cell carcinoma	Moderate	Few	Scant	Scant	—	
Lymphosarcoma	High	Many	—	None	—	
Medullary carcinoma	High	Few	Many	Scant	—	Tumor size of a man's fist; small round cell type and vascular
Duct cell carcinoma	High	Many	Many	Scant	—	Tumor size of hickory nut
Scirrhus carcinoma	Low	Rare	Moderate	Abundant	—	
Colloid carcinoma	Low	Rare	Scant	Scant	—	
Epithelioma	High	Many	Few	Scant	—	Colloid-like material abundant
Medullary carcinoma	Moderate	Few	Few	Scant	—	Pearl-forming epithelioma
Scirrhus carcinoma	Low	None	Scant	Abundant	—	Histologic invasion of muscle
Epithelioma	Moderate	Few	Scant	Little	—	
Duct cell carcinoma	High	Many	Scant	Scant	—	
Duct cell carcinoma	Moderate	Many	Scant	Scant	Axilla	Hemorrhagic cysts in tumor
Tuberculosis and scirrhus carcinoma	Moderate	None	Moderate	Moderate	—	Caseation necrosis and giant cell tubercles; amyloid degeneration of vessel walls
Nevus cell carcinoma	Moderate	Rare	Scant	Scant	—	Tumor of cutaneous origin; roentgen treatment for several months
Adenocarcinoma	Moderate	Few	Moderate	Scant	—	
Medullary carcinoma	High	Few	Moderate	Scant	—	Histologic invasion of muscle, marked
Carcinoma simplex	Moderate	Few	Moderate	Moderate	—	
Myeloma	High	Few	—	Scant	Spine (?)	Size of egg; rapid growth, 2 months; death probably from spine metastasis
Fibrosarcoma	Moderate	Many	None	None	—	Compact embryonic type cells
Scirrhus carcinoma	Low	None	Few	Abundant	—	
Duct cell carcinoma	Moderate	Few	Few	Moderate	Axilla	Calcareous deposits, marked

on the 28 malignant tumors reported at that time, and to them have been added 32 other malignant neoplasms found in the breasts of men. This histopathologic and statistical study is based on a rather unique opportunity for studying, restudying and comparing a collection of histologic sections from 60 cases of malignant tumors of the male breast, and the free use of records pertaining to the cases. Part of this material has been sent directly to me by conferring physicians for diagnosis, but the greater part of it has come through the cooperation of Dr. Burton T. Simpson and the members of his staff at the State Institute for the Study of Malignant Disease, Buffalo.

This group represents material obtained directly from patients going to the surgeon and specimens of breasts submitted to the laboratory for diagnosis by surgeons distributed over the states of Missouri and New York. It, therefore, is more representative of statistical facts and types of lesions than if the material were from one group of surgeons to whom patients with certain classes of disease gravitate, as their reputation is built around a special procedure or treatment.

I have made the grouping and final classification of these specimens of malignant tumors of the male breast and hence they record the impressions of a single observer. This should be of greater value than compilations of records from many sources and many observers, some of whom at least would not hold similar opinions or adhere to a uniform terminology or classification. An effort was made early in the study to learn the outcome of the condition, but because so few answers were obtained from the patients the effort was discontinued.

#### EXPERIMENTAL MATERIAL

This record is based on a pathologic study and comparison of a series of 8,873 lesions of the breast in 106,583 specimens that were submitted to the State Institute for the Study of Malignant Disease, Buffalo, during the period from 1900 to Aug. 26, 1931, and 406 lesions of the breast from 10,433 specimens that have been examined in the Department of Pathology of the University of Missouri School of Medicine, Columbia, between Aug. 1, 1922, and Sept. 10, 1931. Of this total of 117,016 surgical specimens examined in the two laboratories, 9,279 were of the breast, and of this number 308 were from men and 8,941 from women, while in 30 specimens the sex was not ascertained.

*Classification of Lesions.*—Of the 308 male breasts examined, 60, or 19.48 per cent, contained malignant neoplasms. Of these tumors, 50, or 16.23 per cent, were carcinomas, and 10, or 3.25 per cent, were sarcomas. It was found that 105, or 34.09 per cent, of the male breasts contained benign tumors conforming in type to the same class of new growths more regularly found in the female breast. In 143, or 46.42

per cent of the breasts, a diagnosis other than neoplasm was made. Of the total of 308 lesions, 8, or 2.55 per cent, were carcinomas that began in the skin or outer ducts of the nipple; 42, or 13.63 per cent, arose from acinus or duct epithelium, as glandular or duct cell carcinomas, and 10, or 3.25 per cent, were sarcomas.

*Incidence of Types.*—The percentages of different types of growths are at great variance with the opinions generally expressed by other authors. For instance, Speese<sup>2</sup> said that nearly 99 per cent of all neoplasms of the breast occur in the female, and only about 1 per cent in the male. Boyd<sup>3</sup> stated that carcinoma is the most frequent pathologic lesion in the male breast. Deaver and McFarland<sup>4</sup> said: "Approximately 20 per cent of all tumors of the male breast are benign. The vast majority of the remaining 80 per cent are carcinomas—sarcomas are exceptionally rare." Williams'<sup>5</sup> records show that cancers con-

TABLE 2.—*Relative Frequency of Mammary Neoplasms*

Variety	Williams's Group, Both Sexes		Author's Series of 165 Tumors of Breast in Males, per Cent
	Neoplasms in General, per Cent	Neoplasms of Breast, per Cent	
Cancers.....	54.5	77.6	30.50
Sarcomas.....	9.4	4.1	6.06
Nonmalignant neoplasms.....	24.7	15.7	63.60
Cysts.....	11.4	2.6	0.00
Total.....	100.0	100.0	99.96

stituted 77.6 per cent, sarcomas 4.1 per cent, nonmalignant neoplasms 15.7 per cent, and cysts 2.6 per cent. Winslow<sup>6</sup> found that of 102 tumors of the breast, 59.8 per cent were carcinomas, 2.94 per cent, sarcomas, and 37.26 per cent, nonmalignant growths; in his group there were 3 men and all had benign tumors.

It will be seen (table 2) that in this series of new growths carcinomas represent only 30.3 per cent, and that the combined malignant growths were only 36.36 per cent, and the benign tumors, 63.6 per cent. The 165 cases of new growths were only 53.63 per cent of the total

2. Speese, John: Tumors of the Male Breast, *Ann. Surg.* 55:531, 1912.

3. Boyd, William: *Surgical Pathology*, Philadelphia, W. B. Saunders Company, 1925, p. 530.

4. (a) Deaver, John B., and McFarland, Joseph: *The Breast: Its Anomalies, Its Diseases, and Their Treatment*, Philadelphia, P. Blakiston's Son & Co., 1917, p. 518; (b) p. 415; (c) p. 576; (d) p. 481; (e) p. 416; (f) p. 683; (g) p. 390.

5. Williams, W. Roger: *The Varieties of Mammary Neoplasms and Their Relative Frequency*, *Brit. M. J.* 2:576, 1892.

6. Winslow, Nathan: *Tumor of the Breast*, *Bull. School Med., Univ. Maryland* 17:97, 1931.

of 308 cases, and those diagnosed as not involving new growths numbered 143, or 46.42 per cent.

Bryan<sup>7</sup> stated: "One per cent of all tumors of the breast occur in the male, and two per cent of this number are malignant." That only 2 per cent of the tumors of the male breast should be found malignant is so obviously an error of computation or of printing that it seems absurd to call attention to it, except that the statement has already been quoted by other writers. In my group of 165 tumors of the male breast, 36.36 per cent were malignant (carcinomas, 30.3 per cent, and sarcomas, 6.06 per cent).

### CARCINOMA

*General Factors and Statistics.*—Data are recorded on 60 malignant neoplasms. Of these, 50 were carcinomas, 42 were of the gland (acinus) or duct (columnar) cell type and 8 of cutaneous origin (table 4).

TABLE 3.—Group Diagnoses, Percentages and Ratios

Group Diagnoses	Total		Male		Female		Ratio Male to Female
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	
Containing malignant tumors.....	4,125	44.45	60	0.64	4,065	43.80	1:67.75
Containing benign tumors.....	2,429	26.17	105	1.13	2,324	25.04	1:22.13
Seat of cysts, mastitis, etc.; not containing tumors .....	2,551	27.49	140	1.50	2,411	25.99	1:17.22
Necrosis, decomposed, unfixed, etc.; no diagnosis possible .....	144	1.55	3	0.031	141	1.519	1:47.00
Sex not ascertained.....	30	0.32					
Total breasts examined.....	9,279	99.98	308	3.31	8,941	96.35	1:29.03

The average incidence of carcinoma of the breast in men is far below that in women. It is commonly stated that carcinoma is the most frequent lesion of the male breast, but it occurs from 75 to 100 times more often in the breasts of women. In 1876, Wagstaffe<sup>8</sup> tabulated the 60 cases of malignant tumors of the male breast then recorded in the English and foreign medical literature, and reported the sixty-first case, the only one at that time on record in which both breasts of a man were affected. He cited Tauchon as reporting from the "Registers of Paris" that for the eleven year period from 1830 to 1840 inclusive the number of deaths from cancer was 9,118, of which 5 were from cancer of the male breast. In 1919, Fessler<sup>9</sup> reported that approximately 700

7. Bryan, Robert C.: Cancer of the Breast in a Boy Fifteen Years Old, Surg., Gynec. & Obst. **18**:545, 1914.

8. Wagstaffe, W. W.: Scirrhus of the Male Breast; Both Glands Affected, Tr. Path. Soc., London **27**:234, 1876.

9. Fessler, Julius: Der Krebs der männlichen Brustdrüse, Deutsche Ztschr. f. Chir. **172**:429, 1922.

cases of cancer of the male breast were found in the literature, according to statistics compiled from twenty-nine authors. In 11,821 compiled reports of cases of the breast, he noted that 167 lesions were of the male breast and 11,654 of the female breast, which shows 1.41 per cent of carcinomas of the breast occurring in men.

Williams <sup>5</sup> said that malignant neoplasms constitute 81.7 per cent of all neoplasms of the breast, and only 18.3 per cent are nonmalignant. He further said that nearly 99 per cent of all neoplasms of the breast

TABLE 4.—*Histopathologic Types as Found in Sixty Cases of Malignant Tumors of the Male Breast*

	Number of Cases	Per Cent of Total
A. Sarcoma		
Chondromyxosarcoma.....	1	1.66
Fibrosarcoma (small spindle cell).....	5	8.33
Leiomyosarcoma (large spindle cell).....	1	1.66
Liposarcoma.....	1	1.66
Lymphosarcoma.....	1	1.66
Myeloma (myeloid sarcoma).....	1	1.66
Total sarcomas.....	10	16.66
B. Carcinoma		
1. Skin type		
Basal cell carcinoma.....	2	3.33
Melanocarcinoma.....	1	1.66
Nevus cell carcinoma.....	3	5.00
Squamous cell carcinoma (epithelioma).....	2	3.33
Total carcinomas of skin.....	5	13.33
2. Duct and gland cell carcinoma		
Duct cell carcinoma.....	9	15.00
Adenocarcinoma.....	3	5.00
Colloid carcinoma.....	1	1.66
Medullary carcinoma.....	15	25.00
Scirrhus carcinoma.....	9	15.00
Carcinoma simplex.....	5	8.33
Total duct and gland cell carcinomas.....	42	70.00
Total carcinomas.....	50	83.33
Total cases.....	60	99.99

occur in women, and only about 1 per cent in men. Deaver and McFarland <sup>4b</sup> estimated that only 5 per cent of all tumors occurring in men are in the breast, and stated that all writers agree that carcinoma is by far the most common variety of new growth in the male breast.

Our incidence of carcinoma of the male breast as compared to that of the female breast is as 50 to 4,014, a proportion of 1 to 80; thus 1.24 per cent of the carcinomas of the breast occurred in men. Carcinomas, however, occurred only 5 times more often in the male breast than did sarcomas, whereas in the female breast, carcinomas were found 79 times more frequently than sarcomas.



*Age Incidence.*—Deaver and McFarland,<sup>10</sup> in 1917, in the total of the largest series of cases reported during the previous fifty years by fifteen surgeons, found the average age in both sexes to be 50.1 years. In their own series, it was 49.6 years. In a compilation of 401 cases occurring in men, Wainwright<sup>10</sup> found that the age at observation averaged 54.2 years, and stated that in women most cases occur between the ages of 45 and 49, and in men between the ages of 60 and 64; about one half of the women and about two thirds of the men are over 50. The lowest age incidence has been reported as 45.3 years by von Winiwarter,<sup>11</sup> and the highest as 55 years by Finsterer.<sup>12</sup> Bryan<sup>7</sup> gave the mean age for men as 50 years, and for women as 48. According to his record, the disease begins on an average two years later in men

TABLE 5.—*Age Distribution for the 56 Cases in Which Age Was Obtained*

Age Groups	Carcinoma		Sarcoma	
	Number	Per Cent	Number	Per Cent
Up to and including 30 years of age.....	1	2.1	4	44.4
Up to and including 40 years of age.....	7	14.9	5	55.5
Up to and including 50 years of age.....	14	29.8	6	66.6
Up to and including 60 years of age.....	29	61.7	8	88.8
41 to and including 60 years of age.....	22	46.8	3	33.3
41 years of age and over.....	40	85.1	4	44.4
61 years of age and over.....	18	38.3	1*	11.1
71 years of age and over.....	8	17.0	0	0.0
81 years of age and over.....	2	4.2	0	0.0
Number of cases.....	47		9	
Average age.....	57.7		39.7	
Earliest age.....	30		23	
Latest age.....	89		62*	

\* Case of myeloma.

than in women, and also a relatively larger number of cases begin after the age of 70 in men than in women.

In my series of cases, the youngest male patient who had carcinoma was 30 years of age, and the oldest was 89, while the average age for the group was 57.7. This is higher than the average age as given by other authors. It is to be noted (table 5) that only 29.8 per cent of the cases developed before the fifty-first year of age, 85.1 per cent after the forty-first year, 38.3 per cent after the sixty-first year, and 17 per cent after the seventy-first year. This is significant of the rôle that age plays in male mammary carcinomas. This study showed an

10. Wainwright, J. M.: Carcinoma of the Male Breast, Arch. Surg. **14**: 836 (April) 1927.

11. von Winiwarter, A.: Beiträge zur Statistik der Carcinome, Stuttgart, Ferdinand Enke, 1878.

12. Finsterer, J.: Zur Pathologie der männlichen Brustdrüse mit besondere Rücksicht der Tumoren, Deutsche Ztschr. f. Chir. **84**:201, 1906.

average age for the development of sarcoma of 39.7 years; hence the carcinomas as a group began on an average eighteen years later in life than did the sarcomas.

*Duration of Tumor at Time of Operation.*—In the 3 carcinomas of the skin for which the duration was stated, the greatest time that elapsed from the first knowledge the patient had of the tumor until operation was three years, and the shortest time was several months. In the 24 gland or duct cell types, the longest period was four years and the shortest from three to four weeks, with an average of about fifteen months. For the carcinomas as a whole, then, the longest period was four years and the shortest from three to four weeks, with an average of about fifteen months.

*Trauma.*—There was a definite history of trauma in only 4 cases. In case 31487, one of nevus cell carcinoma, it was stated that for several years the left breast had become sensitive, sore to touch and often swollen during cold weather, and that during the winter prior to observation, from six to eight months previously, this condition did not clear up as it had formerly done. There occurred a breaking out of the skin which spread to the size of a dime and thickened, forming a lump. In case 33219, one of carcinoma simplex, there was a history of repeated trauma to the breast. After an injury to it one year prior to examination there developed a hard, painful lump which continued to grow. In case 25-20M, one of medullary carcinoma, the patient had for many years done cabinet woodwork and modeling of bird houses and toys. He often bruised his right breast while using drawing knives, jack planes and similar tools. In case 26642M, one of a duct cell carcinoma which arose at the outlet of the nipple, there was a statement that in an injury eight months prior to operation the patient was thrown against a farm implement, and his breast struck a sharp prong on a spreader. Afterward he noticed blood on his clothing and a break in the skin covering the nipple. Several weeks later he noted a painless lump in the nipple.

*Breast Involved.*—The breast involved was the left in 14 instances, and the right in 10; no statement was made in 26 cases. The positive facts here signify little, for in more than one half of the cases the breast involved is not known.

*Location in Breast.*—Statements as to the place of origin in the breast or as to where the growth was found at operation are of little significance, for in only 8 cases was this information obtained. In these, the growth was recorded as beginning at the outlet of the nipple, at the margin of the nipple, near the edge of the breast, in the substance of the breast and below the margin of the nipple; in one case the nipple was over the center of the tumor, in another the tumor was

stated to have arisen in the skin over the breast, and in the eighth, case 15889, there was a clinical diagnosis of epithelioma of the nipple, which placed the tumor definitely as involving that part.

*Size of Tumor.*—The referring surgeons described the growths in relation to size in the following terms: a  $1\frac{1}{2}$  inch mass, an 8 by 16 cm. tumor, a growth the size of an egg, a nodule and a tumor twice the size of the breast, the size of a silver dollar, the size of a hickory nut or twice the size of a pigeon's egg. In 42 instances there was no mention of the size of the tumor.

*Rate of Growth.*—No specific statement was given in 45 cases as to the rate of growth, but from the duration of the tumors and their respective sizes, one may get some idea as to their growth energy. In 1 case, the tumor was stated to be of gradual growth, in 2 cases of slow growth and in 1 case of slow growth but perceptibly increasing for two months, and in the fifth instance it was said to have grown more rapidly during the past year.

*Discharge from Nipple.*—In only 3 instances was there a statement concerning discharge from the nipple, and the discharge was recorded as bloody in 1 case and as serous in 2 cases.

*Ulceration.*—Statements concerning ulceration were not made for any of the specimens. In the laboratory examination, ulceration of the surface-covering skin was described in 3 cases that were not of cutaneous origin.

*Involvement of Muscles.*—In 1 case, the record stated that there was gross invasion of the pectoral muscle, and histologic preparations revealed muscle bundles invaded by cancer cells in 7 other cases. Sections were not taken particularly for the purpose of showing involvement of the muscles, but primarily for diagnosis, and this observation therefore was incidental. Under a planned search, it is not doubted that muscle invasion would be found in a high percentage of malignant growths of the male breast.

*Metastasis to Axillary or Other Tissue.*—In 13 instances involvement of the axillary nodes was present at operation (histologic confirmation or diagnosis). In one of these there were also metastatic cutaneous nodules over the thorax. At death 3 of the 13 patients had metastatic involvements of the lungs, liver, axillary nodes and skin. In 1 instance there were metastases only in the skin of the corresponding arm, and at death there was generalized carcinomatosis. One patient had cutaneous nodules over the thorax, and another had involvement of the group of lymph nodes behind the pectoral muscles. Two patients who had no involvement of the axillary nodes at operation had general metastases to visceral organs at death. Metastases were present at

operation in 16 of the 50 cases of carcinoma of the male breast. This is indicative of the negligence, indifference and procrastination of men. As was to be expected, the basal cell types showed neither invasion of muscle tissue nor metastases in the axillary nodes or elsewhere.

*Previous Treatment.*—Only 2 patients gave a history of having had any form of treatment before coming to the operator who submitted the specimen for diagnosis. One patient (case 29641) had had his breast removed because of a tumor five months previously, in Russia. Laboratory examination of the recurrent tumor showed gross and histologic involvement of the muscles and axillary lymph nodes. The patient died a few months later with generalized metastases. The other (case 91540), who had a nevus cell carcinoma, had received roentgen treatment for several months with no appreciable beneficial results.

*Clinical Diagnosis.*—The general belief that carcinoma is the most common lesion of the male breast is reflected in the frequency with which the clinical diagnosis of carcinoma was made. Of the 50 cases, in 34 the clinical diagnosis was carcinoma; in 2, cancer; in 3, a malignant growth, and in 1, epithelioma of the nipple. Thus, in 30 cases the condition was labeled by the surgeon as malignant. Of the remaining 20 cases, no opinion was given on 14; in 2 the diagnosis was tumor, and under each of the following terms 1 was classified: growth, fibroma, syphilis and chronic mastitis. It is probable that the late stage in which these tumors of the male breast were seen and their fixation to skin, muscle or thorax were the reason for the high number of clinically correct diagnoses made.

#### PATHOLOGY OF CARCINOMA OF THE MALE BREAST

Deaver and McFarland<sup>41</sup> listed fifty-four terms that have been variously used in the diagnosis of carcinoma of the breast, and invited simplification of nomenclature. In this paper the terms will be confined to a simple classification, and the use of unnecessary and complicating terminology eliminated. From the standpoint of anatomic origin and histologic types of tissue, the group of carcinomas is divided into: first, those that originated in the skin or the outer ducts where the lining cells are more or less transitional in type and often produce growths that to all appearances are composed of skin type cells, and second, those that arose from definite duct (columnar) lining cells, or acinus (glandular) type cells.

*Skin Type Carcinoma.*—Williams,<sup>13</sup> in 1889, recorded 3 cases of cancer of cutaneous origin in his 2,422 cases of mammary carcinoma.

13. Williams, W. Roger: Cancer of the Male Breast, Based on the Records of One Hundred Cases, *Lancet* 2:261 and 310, 1889.

He stated that the condition is exceedingly rare in both sexes and that Billroth had denied its occurrence in the female breast, but that Czerny had later recorded a case, the only one of the kind then on record.

A striking feature of the histologic study of the 50 carcinomas here recorded is found in the 8 instances, or 16 per cent, in which the origin was in the skin or the outer ducts (table 4). There is further a marked incidence of nevus cell carcinomas and of the pigmented type, or melanocarcinomas; 4 occurred in this group of 8 tumors of the skin. This frequency of primary growths arising from the skin may be explained by the fact that in the male subject the tumors of the skin in general are more often encountered than in the female; by the fact that the skin over the male breast has not the buffer or bed of protective elastic tissue and fat beneath it that is present in the female organ and therefore is affected more readily than the female breast by surface irritation and injury; by occupational injuries and insults, and by the difference in clothing. It will be recalled that cancer of the female breast, prior to the emancipation of that organ by the advent of the corsetless era, was 10 times more common among women who wore corsets than among those who did not. If this is true, does it not make a difference whether a man wears suspenders or garments like overalls with a buckle or button located near the breast, where movements of the body produce repeated friction or irritation, and where objects carried in the arms add further irritation?

**Basal Cell Carcinoma (Rodent Ulcer):** Two cases showing all the typical features of basal cell carcinoma were seen. They conformed to the true type of this new growth (fig. 1) as it is most commonly found about the face. The absence of the lymphocytic cell infiltration, pearl formation and hyalinization seen in epitheliomas, with the presence of the small, less distinctly defined walls and basic staining of the cells, the tendency to form alveolus-like spaces, the "point lace" basal edge outline and the sharpness of the tumor margin, bespeak an entirely separate group from the epitheliomas. In neither of these 2 cases was involvement of muscles or metastasis to the axilla or elsewhere recorded.

**Nevus Cell Carcinoma and Melanocarcinoma:** In this group of 3 cases of nevus cell carcinoma and 1 of melanocarcinoma, the histologic picture showed cells of a type and pigmentation that made it evident that the growths were not epitheliomas or basal cell carcinomas, but were of epithelial origin like the benign nevi seen in other locations. Three of the cases showed a small amount of pigment, whereas in the other there was a massive amount. For this reason the growths were diagnosed differently, although the opinion is held that they represented the same type of tumor and differed only as to degree of pigment.

Sections showed a tumor having peripheral growth and a lobular appearance. The lobulations were made up of closely packed cells, with varying amounts of intervening stroma. There was little stroma within the lobulated-appearing cell masses, and between these masses in some instances it was scant and in others abundant. The cells of the masses



Fig. 1 (case 47200).—Basal cell carcinoma.

appeared epithelial, small and closely fused, and were thus less distinct than in epitheliomas. While the cell outlines were not distinct, the nuclei were. In one instance the cells appeared much like those of an endothelioma, and, to carry the similarity further, there were alveolus-like formations or small, cystlike spaces containing a bluish-staining material like a secretion, resembling similar areas of the endotheliomas.

In the melanocarcinoma there was a massive amount of pigment in the primary tumor (fig. 2) and in the metastases to the axillary lymph

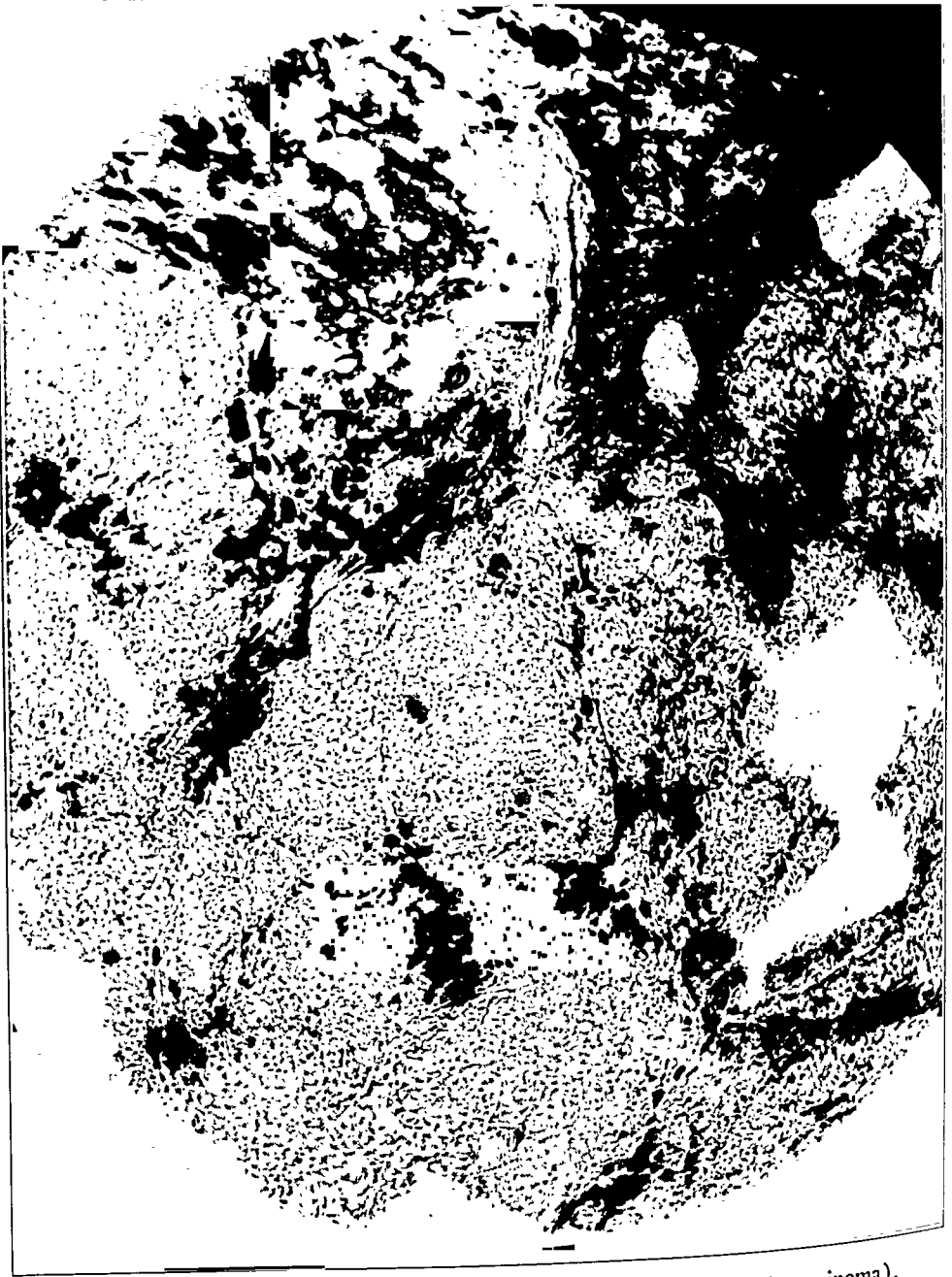


Fig. 2 (case 21502).—Melanocarcinoma (pigmented nevus cell carcinoma).

nodes. Much of the pigment was in the heavy bands of stroma as well as within tumor cells. This tumor contained many mitotic cells, and it was graded as highly malignant.

In one of the cases in which the tumor was designated as a nevus cell carcinoma, no mitotic cells were seen and the stroma was extremely vascular. The patient died within six months after operation from extensive metastases. In another case the patient had previously received roentgen treatments for several months. In this instance mitoses were rare, and the stroma was scant.

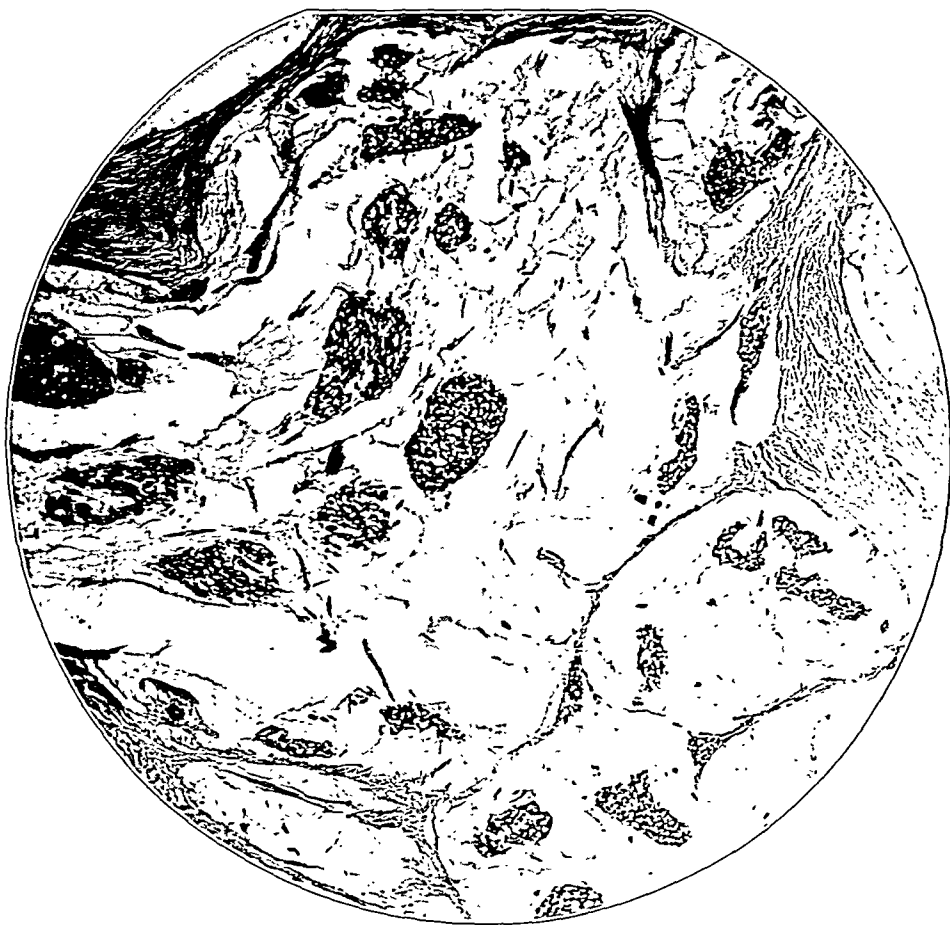


Fig. 3 (case 68376).—Colloid carcinoma.

Epithelioma: The 2 cases recorded as instances of squamous cell carcinoma showed nothing unusual or different from these tumors as they are encountered elsewhere. Both showed a tendency toward pearl formation, invasive, penetrating and branching prolongations, detached cell nests, mitotic cells and an infiltration of lymphocytes around their borders which even invaded the periphery of the growth. This factor of lymphocytic invasion, forming often a more or less definite marginal



zone of the tumor, is one that is too often overlooked in the diagnosis and differential diagnosis of squamous cell carcinoma.

*Duct and Gland Cell Carcinoma.*—Forty-two, or 84 per cent, of the carcinomas were placed in this general group. Nine of them had a cell content sufficiently like the columnar or duct cell type that they could

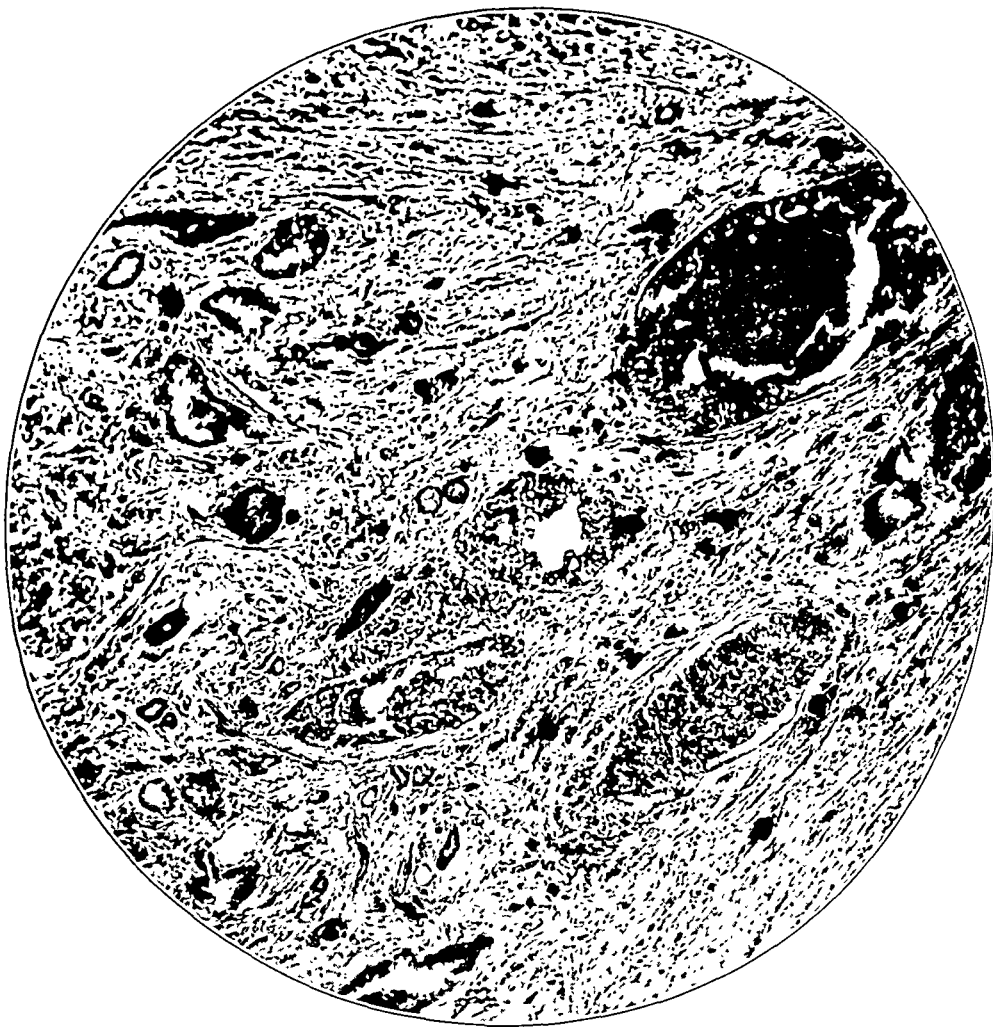


Fig. 4 (case 103408).—Duct cell carcinoma (columnar cell), showing calcareous deposits.

be grouped as duct cell carcinomas. The other 33 were of the acinus or gland type cell, although areas in some of them were much like the duct cell variety.

*Duct or Columnar Cell Carcinoma:* In these tumors the general features of an atypical, organoid neoplasm were found. In many areas there was the appearance of a gland (acinus) cell carcinoma, but in

greater areas, the cancer cells were definitely columnar and were often seen in deposits of single layers either lining spaces, such as ducts (figs. 4 and 5), or as multiple layers surrounding projections of stroma. The cells nearest the stroma were clearly columnar, while the more superficial or older cells appeared more irregular. Many of the ill formed ducts had two or more layers of these cells; often a ductlike space was

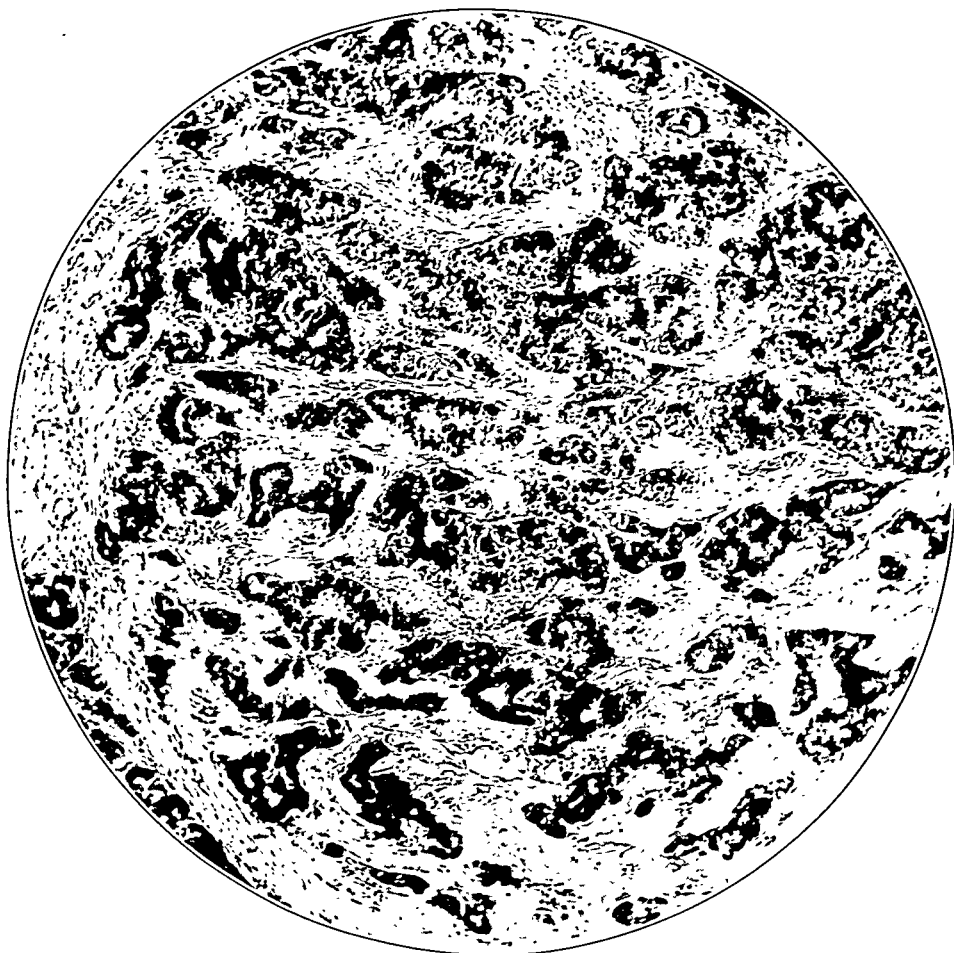


Fig. 5 (case 84686).—Duct cell carcinoma.

filled or obliterated by the many cell layers. Those in the center of the space not rarely showed necrotic changes or had broken down to form a granular material. In this group of 9 cases no effort was made to divide the growths into scirrhous, medullary or simplex types.

Adenocarcinoma: The features that led to the coining of the term adenocarcinoma and its perpetuation were so pronounced in 3 cases as to warrant its use in their diagnosis and classification. These 3 showed

definite attempts at glandular formation, such as is seen in adenomas, but the growths were atypical and therefore were carcinomas.

Colloid Carcinoma (Mucoid Carcinoma, Carcinoma Gelatinosum): In 1 case only were there encountered the degenerative changes that lead to this type of tumor. In this instance (fig. 3) there were islands of small cells containing hyperchromatic nuclei, and filling the wide spaces around these groups were an acidophilic staining material and a scant stroma. Within several small lymphatics tumor cell masses were found.

Medullary Carcinoma, Scirrhus Carcinoma and Carcinoma Simplex: Irrespective of the general use of the terms medullary, scirrhus and simplex as guides to the proportion between stroma and cancer cells, it is felt that it is unwise to depend on this factor alone for special classification and as an index to the degree of malignancy. To use this as a

TABLE 6.—*Comparison of Histologic Types of Carcinoma as Recorded by Other Authors*

Variety of Cancer	Warren's <sup>14</sup> Group (Female)		Wainwright's <sup>10</sup> Group (Male)		Author's Group (Male)	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Paget's disease.....	1	1.00	0	0.00	0	0.00
Colloid (gelatinous).....	2	2.00	3	3.70	1	2.00
Adenocarcinoma.....	3	3.00	13*	16.60	3	6.00
Scirrhus.....	28	28.00	38	49.00	9	18.00
Carcinoma simplex†.....	26	26.00	3	3.70	5	10.00
Medullary.....	40	40.00	14	18.00	15	30.00
Duct cell.....	0	0.00	0	0.00	9	18.00
Squamous or basal cell.....	0	0.00	7†	9.00	8	16.00
Total.....	100	100.00	78	100.00	50	100.00

\* Includes three malignant duct papillomas.

† Includes one basal cell carcinoma.

‡ Warren's group, "cancer."

final basis for adjudication would necessitate histologic examination of many widely separate portions of tumors. This is evident to pathologists who regularly see sections from a carcinoma showing the characteristics of the scirrhus type, while other sections taken elsewhere, especially from the margin of the growth or from its metastatic processes, yield the features of the medullary type.

In this classification the term carcinoma simplex is used according to general custom; that is, for a type of carcinoma having a histologic balance of cancer cells and stroma to a degree between the medullary and scirrhus types. In the original table of Warren,<sup>14</sup> which is used for comparison in table 6, he does not use the term carcinoma simplex, but groups 26 cases merely under the term "cancer." Since he employs the terms medullary and scirrhus, it is presumed that these 26 tumors

14. Warren, J. Collins: The Operative Treatment of Cancer of the Breast. *Ann. Surg.* 40:805, 1904.

constituted a group that could not be placed in either of these types, and hence that group has been compared to those that I have termed carcinoma simplex.

It seems unnecessary to record what is meant by medullary or scirrhous carcinoma or carcinoma simplex. Under these classifications are grouped all forms of glandular cell type carcinomas not included as adenocarcinoma or colloid carcinoma. They conform in all essentials to the same types that occur more commonly in the female breast, with the exception that in this group of carcinomas of the male breast there was practically no effort at cystic formation and little attempt at acinus or gland production. This is the only outstanding difference noted.

*A Case of Tuberculosis and Carcinoma in a Male Breast.*—Case 90476, diagnosed by Dr. A. A. Thibaudeau, pathologist, State Institute for the Study of Malignant Disease, Buffalo, represents a rare, if not unique, condition in the breast of a man. The sections of this organ revealed a definitely characteristic scirrhous carcinoma which on histologic examination showed a moderate degree of malignancy, moderate lymphocytic infiltration and a moderate amount of stroma. In addition, they contained areas of caseation necrosis surrounded by cellular walls composed of lymphocytes, endothelial leukocytes (epithelioid cells) and foreign body giant cells; Langhans' giant cell tubercles, and an amyloid deposit in the walls of the arteries and arterioles. The areas of caseation necrosis and tubercles occurred largely in the stroma lying between rows or nests of cancer cells. No tuberculous lesions were found within groups of cancer cells. Unfortunately, sections of the tissue were not available for the application of a special stain for acid-fast bacilli, nor was unfixed tissue available for culture or animal inoculation. While the crucial bacteriologic proof of tuberculosis is out of the question, the condition shown by this specimen has been diagnosed as tuberculous on the basis that caseation necrosis, Langhans' giant cell tubercles and amyloid degeneration were present and in themselves sufficient for that diagnosis. It would have been of much interest and scientific value to have been able to follow this patient, but although the operation was performed as late as May, 1930, several recent communications addressed to the physician have brought no response.

Swan and Fry,<sup>15</sup> in 1926, tabulated 11 cases from the literature and reported a twelfth case of tuberculous mastitis in a male subject. They stated that, including those seen in the male, less than 200 cases had been reported. Morgen<sup>16</sup> recently recorded (November, 1931) the twentieth case of tuberculosis of the male breast, and stated that in the literature he had found in the two sexes more than 439 cases of mammary tuberculosis. It is of interest to note in the article by Swan and Fry that of the 12 approved cases in the male breast, tubercle bacilli were found in only 3 instances, and animal inoculation gave positive

15. Swan, R. H. Jocelyn, and Fry, H. J. B.: Tuberculosis of the Male Breast, Brit. J. Surg. 14:234, 1926.

16. Morgen, Maximilian: Tuberculosis of the Breast, Surg., Gynec. & Obst. 53:593, 1931.

results in 1 of these 3. Thus, in 9 of the 12 cases the diagnosis was made without the finding of the organisms or the obtaining of a positive reaction in an inoculated animal.

*A Case of Carcinoma of the Male Breast with Bronzing of the Skin and Extreme Generalized Metastases at Autopsy.*—Only the salient features and pertinent autopsy observations in this case will be recorded.

D. D. M., aged 69 (case 25-20M), was operated on by Dr. Frank G. Nifong at the Boone County General Hospital, Columbia, Mo., on Jan. 9, 1925, for carcinoma of the right breast. He was a farmer, but for several years had spent much time in woodwork, making toys, bird houses, small cabinets and similar articles. In this work he had often bruised the tissues of the right side of the chest.

For several years prior to operation he had noticed a lump the size of a hazelnut in the right breast. This was never painful and had not increased in size



Fig. 6 (case 25-20M).—*A*, lateral roentgenogram of thorax, showing metastatic tumor in mediastinum. *B*, roentgenogram showing intrathoracic metastases.

until about two months previously, when it began to show perceptible growth. On examination there was found a movable, hard tumor having two apparent nodules the size of pigeon's eggs, under and below the nipple. It was attached to the nipple, and the skin over the tumor was dimpled. The breast and tumor were removed by a wide excision, the nipple and all tissue down to and including the pectoral muscles and fascia being removed.

The pathologist's report (M. P. N.) stated that on gross examination there was a firm, white nodular tumor immediately beneath and lateral to the nipple. Histologically, the growth was an atypical, organoid neoplasm of glandular type epithelium, with a tendency for the tumor cells to be arranged in tubular forms, but supported by a scant stroma. Mitotic cells were present in moderate numbers, and around the periphery of the tumor there was a small amount of lymphocytic infiltration. The diagnosis was medullary carcinoma.

On June 3, 1926, the patient presented himself, stating that there had been a gradual increase of a growth which had appeared in the scar shortly after the

operation seventeen months before. The right mammary region was now the site of a mass having a base from 10 to 12 cm. in diameter and elevated about 5 cm. It was hard, bluish at the center and apparently ready to break down. The mass was movable above the ribs, and there were no palpable glands in either axilla.

A second operation was performed on June 4, 1926. The tumor was removed by electric cautery, a circle about 30 cm. in circumference being made. The mass was entirely ablated, and the soldering iron was used to sear the raw surfaces and to cauterize the base. No knife was used, and no vessels were tied.

The pathologist's report (M. P. N.) stated that the skin-covered tumor 4 by 6 by 10 cm. was surrounded at its edges by adipose tissue and rested on muscle. Microscopically, the tumor cells were predominant over stroma and extended down to and between the sheaths and bundles of muscle fibers. The cells were



Fig. 7 (case 25-20M).—Aorta, esophagus and longitudinally divided trachea, showing marked metastases to lymph nodes.

large and embryonic in appearance. The diagnosis was a very active medullary carcinoma.

On June 18, 1929, the patient presented himself and stated that a few days before he had noticed a nodule below the old scar near the right breast. The nodule was freely movable, oval and within the skin. No other nodules were found, and there was no evidence of axillary involvement.

A third operation was performed on June 19, 1929. There was removed by electric cautery a nodule the size of a filbert at the lower median quadrant of the area of the right breast.

The pathologist's report (M. P. N.) stated that the growth was an oval segment of skin 1.5 by 2.5 cm. covering a firm, white, irregular nodule 1 by 1.4 cm. The edges of the tumor extended to the margin of the specimen of tissue. The diagnosis was glandular cell scirrhus carcinoma with a rather definite wall of lymphocytes surrounding the periphery.

Examination on April 22, 1930, showed: During the past few months the patient had lost about 25 pounds (11 Kg.) in weight and had become feeble; he now suffered from dyspnea. There was some enlargement in the scar over the right ninth costal cartilage; otherwise the scar was pliable and movable. Above the clavicles were felt many small lymph nodes in both sides of the neck. Some were as large as a filbert and closely attached to the clavicles. The axillary glands were not much involved. Roentgenograms (fig. 6) revealed extensive involvement of the lungs and mediastinum.

On Dec. 16, 1930, the patient died, almost six years after the primary operation.

The autopsy observations were as follows: There were general emaciation, bronze pigmentation of the skin, hemoperitoneum, bilateral hemo-



Fig. 8 (case 25-20M).—Lung, showing marked metastases to lymph nodes at its hilus.

thorax, hemopericardium and ulcerated recurrent carcinoma of the right side of the thorax. There were carcinomatous metastases: in the skin of the right side of the thorax, parietal peritoneum, right axillary lymph nodes, right infraclavicular and supraclavicular lymph nodes, retroperitoneal and lymph node group near the right kidney and bilateral tracheobronchial lymph nodes (extensive); in the hilus of the lung (fig. 8) (bilateral); in the peritracheal, periesophageal and periaortic (thoracic) lymph node groups (fig. 7) (bilateral); in the manubrium and gladiolus sterni, with softening and deformity; in the left first, second, third, sixth, seventh and eighth costal cartilages, the right first, second, third, fourth, fifth and seventh costal cartilages and the left and right intercostal soft tissues, from the first to the eighth inclusive; in the dome of the right side of the thoracic cavity and extending as a growth over the anterior surface of the aorta and pericardium; in the right side of the visceral and parietal

pleura in the visceral pericardium and lungs (bilateral) (fig. 9); in the liver and suprarenals (bilateral); in the mediastinal soft tissues and the serosa of the stomach, with a direct extension beneath the skin of the thorax, across the sternum, forming a mass in the left infraclavicular space over the first to fourth left costal cartilages.

*Calcareous Deposits.*—In case 103408 (fig. 4), one of a duct cell carcinoma, within the ductlike lumina, and often in otherwise obliterated spaces lined by several layers of cells, were found basic-staining blue bodies. These had a laminated appearance, some rings being lighter and others darker in their staining reaction. They suggested corpora amylacea as seen in the prostate, the lungs and some parotid tumors. It

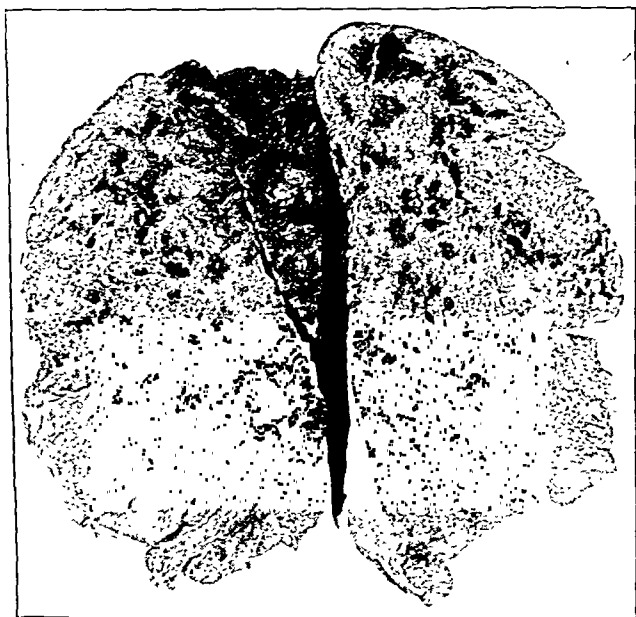


Fig. 9 (case 25-20M).—Bisected lung, showing marked pulmonary metastases and emphysema.

is believed that they were not formed as any part of a degenerative or necrotic change, but were the result of retained secretion within these newly formed spaces, and that the retention was followed by this calcium deposit from the secreted products of the cells. A similar condition was present in the acinus-like spaces of 2 of the adenocarcinomas (cases 6329 and 13639). Many of the ill formed glands in these 2 tumors were filled with a homogeneous, faintly blue basic-staining material like pseudomucin, and in others there were granular calcium deposits.

*Mitosis.*—Following a careful observation of the sections of this group of 50 carcinomas for evidences of rapidity of growth and degree of malignancy as revealed by the presence and number of mitotic cells,



the results were: In 9 instances no mitotic cells were found; in 9 they were present, but rare; in 21 they were present but few, and in 11 they were present in large numbers.

*Lymphocytic Infiltration.*—A marked histologic feature of the epitheliomas and of the entire group of duct or gland cell carcinomas was the evident and marked lymphocytic infiltration (fig. 10). Many sec-

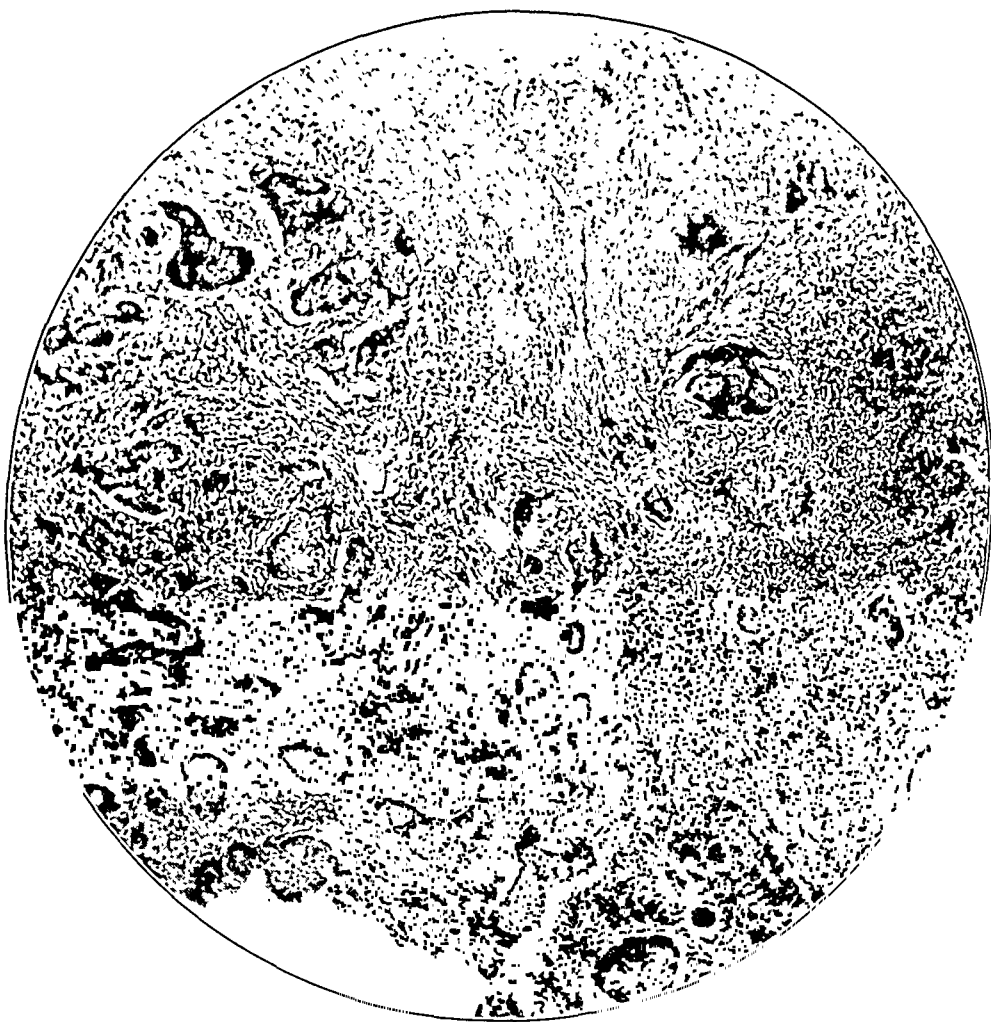


Fig. 10 (case 51431).—Scirrhus carcinoma with massive lymphocytic infiltration.

tions showed the heavy small round cell infiltration. The amount of lymphocytic invasion recorded was as follows: scant in 14 instances; in small amount in 2; showing a few lymphocytes in 8; moderate in 7; abundant in 11, and presenting myriads of lymphocytes in 1. These are exclusive of the nevus cell and basal cell carcinoma groups in which lymphocytic infiltration was practically absent.

*Stroma.*—The amount of stroma is not particularly recorded here for epitheliomas or basal cell carcinomas, for it plays no part in these types. In the nevus cell types and those of duct or acinus cell origin, it is of some significance. In these, the amount of stroma present was scant in 24 instances, about equal in amount with the cancer cells in 4, moderate in 10 and abundant in 8.

*Degree of Malignancy.*—All the histologic factors being taken together, malignancy thus adjudicated has been recorded in only three degrees, as it was believed that this was more accurate and more desirable than to try to divide the group here termed "moderate" into two sub-groups. As the result, 14 tumors were rated as presenting a high degree, 25 a moderate degree, and 11 a low degree of malignancy. Among those rated as of high grade malignancy are the melanocarcinoma and one of the epitheliomas. The group of low grade types contains the 2 basal cell carcinomas and the colloid carcinoma.

These cases as a group show a high degree of malignancy, which is contrary to the generally made statement that carcinomas of the male breast are most often of the scirrhus type and of low grade malignancy. The reason for this relatively high degree of malignancy probably lies in the greater reversionary metamorphosis of the male breast toward a less differentiated, more embryonic type of cells. The high incidence of duct cell carcinomas herein recorded indicates such a change in the male breast, and it is to be recalled that the incidence of this type of cancer in women as recorded is much less than that seen in this male group.

#### SARCOMA

*General and Statistical Factors.*—Of the 60 neoplasms here recorded, 10 were sarcomas. A case of myeloma is grouped under the general term sarcoma, because although the growth would doubtless be termed a mixed round cell sarcoma by some pathologists, it is classed as a sarcoma of bone or bone marrow by most. In the 10 cases of sarcomas (table 4) there were 5 cases of fibrosarcoma, and 1 case each of leiomyosarcoma, liposarcoma, lymphosarcoma, myeloma and chondromyxosarcoma.

*Incidence.*—The general impression is that the average incidence of sarcoma of the breast in men slightly exceeds that in women. It has been stated<sup>16</sup> that mammary sarcoma is approximately 30 times more frequent in women than in men, and that sarcoma is next in frequency after carcinoma among tumors of the male breast. Contrary to this, Schuchardt<sup>17</sup> found that in 472 collected tumors of the male breast, 385

17. Schuchardt, B.: Weitere Mittheilungen zur Casuistik und Statistik der Neubildungen in der männlichen Brustdrüse, Arch. f. klin. Chir. 41:64, 1891; 31:59, 1884; 32:277, 1885.

were carcinomas, 19 were sarcomas and 68 were benign growths, and Williams<sup>13</sup> found 16 carcinomas, 3 sarcomas and 6 benign growths in a series of 25 cases of tumor of the breast in men. It has been estimated that only 5 per cent of all tumors in men occur in the breast, and all writers agree that carcinoma is by far the most common variety of new growth in the male breast.<sup>14</sup>

The data on the group recorded in this paper vary markedly from these statistics. The incidence of sarcoma of the male breast compared to that of the female breast was 10 to 51 (table 8); thus 19.61 per cent of the sarcomas of the breast occurred in men. The ratio between carcinoma of the male breast and that of the female breast was 50 to 4,014. In other words, it was found that there were 10 sarcomas to 50 carcinomas in the male breast, and in the female breast there were

TABLE 7.—*Comparison of Histologic Types of Sarcoma as Recorded by Connell*

Variety	Connell's <sup>15</sup> Statistics (Male Breasts)		Author's Group (Male Breasts)	
	Number	Per Cent	Number	Per Cent
Spindle cell sarcoma.....	12	46.1	6*	60.0
Round cell sarcoma.....	7	26.9	2†	20.0
Ochloroma.....	1	3.8	0	0.0
Cystic sarcoma.....	3	11.5	0	0.0
Melanotic sarcoma.....	3	11.5	0	0.0
Chondromyxosarcoma.....	0	0.0	1	10.0
Liposarcoma.....	0	0.0	1	10.0
Total.....	26	99.8	10	100.0

\* Includes five cases of fibrosarcoma and one of leiomyosarcoma.

† Includes one case of myeloma.

51 sarcomas to 4,014 carcinomas. Carcinomas, therefore, occurred in the male breast only 5 times more often than sarcomas, while carcinomas in the female breast were 79 times more frequent than sarcomas. As compared with the number of carcinomas in the breasts of the two sexes, sarcomas occurred proportionately almost 16 times more often in the male than in the female breast.

Carcinoma was found in this group not to be the most frequent lesion of the male breast, and, likewise, sarcoma has been found not to be the second most frequent. In the group of 165 tumors of the male breast, sarcomas constituted only 6.06 per cent, while the benign tumors amounted to 63.6 per cent. This is contradictory to the incidence reported in the literature, and is a fact that should be borne in mind, for it means that under present diagnostic requirements, 2 of 3 tumors of the male breast are benign.

While sarcoma of the female breast occurs in from 1 to 2 per cent of the cases, it is generally regarded as a great rarity among men. In

TABLE 8.—*Statistical Comparison with Previous Reports*

Year	Author and Reference	Total Number Breasts Recorded	Number Breasts with Malignant Condition	Number Male Breasts				Number Female Breasts			
				Total	Carcinoma	Benign Tumors	Not Tumors	Total	Carcinoma	Benign Tumors	Not Tumors
1889	Williams 13 .....	2,422	1,974	25	16	3	6	2,397	1,863	92	442
1889 (?)	Marsden, Alexander, cited by Ellascheff, Leo: Ueber Krebs der männlichen Brustdrüse, Würz- burg, J. S. Seelmeier, 1891.....	4,356	4,356	75	75	..	...	4,281	4,281	..	.....
1890 (?)	Gurtl, E., cited by Ellascheff, Leo: Ueber Krebs der männlichen Brustdrüse, Würzburg, J. Seel- meier, 1891 .....	1,440	1,440	8	8	..	...	1,432	1,432	..	.....
1891	Schuchardt 17 .....	472	401	472	385	19	68	.....	.....	..	.....
1913	Prinrose, A.: Am. J. M. Sc. 145: 100, 1913.....	323	216	7	4	1	2	316	208	3	105
1922	Fessler 9 .....	11,821	11,821	107	107	..	...	11,654	11,654	..	.....
1925	Kettle, E. H.: The Pathology of Tumors, New York, Paul B. Hoeber, Inc., 1925, p. 31.....	8,428	8,428	61	61	..	...	8,367	8,367	..	.....
1926	Judd and Morse: Surg., Gynec. & Obst. 42: 15, 1926 .....	1,768	1,768	17	17	..	...	1,751	1,751	..	.....
1930	Pfahler, G. E., and Parry, L. O.: Results of Roentgen Therapy in Carcinoma of Breast, J. A. M. A. 94: 101 (Jan. 11) 1930.....	939	939	12	12	..	...	927	927	..	.....
1930	D'Aunoy and Wright 19 .....	68	68	...	...	5	...	.....	.....	63	.....
1930	Neal and Simpson 1 .....	5,314*	2,424	152†	28	7	60	5,132	2,357‡	32	1,568
1931	Author's present group.....	9,279*	4,125	308†	50	10	105	8,941	4,014§	51	2,552#

§ Includes 140 ungrouped cases.

¶ Includes 3 cases of endothelioma.

# Includes 141 ungrouped cases.

\* Includes 30 cases in which sex was not given.

† Includes 3 ungrouped cases.

‡ Includes 2 cases of endothelioma.

1907, Connell<sup>18</sup> found only 34 cases of sarcoma of the male breast in the literature. In 1930, D'Aunoy and Wright<sup>19</sup> reported that their 11 cases added to those previously authenticated brought the number of mammary sarcomas in both sexes to 503.

The relative singularly higher incidence of sarcomas as contrasted to carcinomas in the male breast and the much higher incidence of them than in the female breast may be accounted for by the following facts: (a) In the adult male breast the glandular elements are very scant or absent, and therefore malignant tumors of this cell type are proportionately fewer than in the female; (b) the male breast is rich in connective tissue elements and scant in epithelial elements, including even the number and development of its ducts; (c) trauma or irritation, if and when it plays a part, stimulates the abundant connective tissue to a greater degree than it does the scant epithelial elements (it is acknowledged that connective tissue responds more readily and to a greater variety of irritants than do parenchymatous epithelial cells); (d) the benign prototypes of these malignant connective tissue tumors have been found by Neal and Simpson<sup>1</sup> to be of higher incidence in the male than in the female breast (the ratio was 12 benign connective tissue tumors to 45 fibro-epithelial tumors [adenomas, fibro-adenomas, etc.] in men, as compared to 52 benign connective tissue tumors to 1,479 fibro-epithelial tumors in women).

*Duration of Tumor at Time of Operation.*—At the time of operation on the 10 sarcomas, the tumors had been present for one year, fourteen months, two years and three years, respectively, in 4 cases, and the duration was not stated in 6 instances. In the 4 cases in which the lapse of time was given, the longest period was three years, the shortest, one year, and the average, twenty-one months.

*Trauma.*—In a single instance was there given a history of trauma to the breast in which the tumor developed. In this case the injury occurred fourteen years prior to the time the tumor was noted.

*Breast Involved.*—In two instances the tumor originated in the right breast and in two, in the left; in 6 instances specific mention was not made of the breast in which it originated.

*Location in Breast.*—In 1 case it was stated that the tumor was located in the subcutaneous tissue of the breast; in another it was attached to the fascia; in the liposarcoma the attachment was behind the nipple and areola, and in the case of myeloma "the tumor was beneath the breast, apparently attached to the chest wall, and involved the

18. Connell, F. Gregory: Sarcoma of the Male Breast, Surg., Gynec. & Obst. 4:13, 1907.

19. D'Aunoy, Rigney, and Wright, Roy W.: Sarcoma of the Breast, Ann. Surg. 92:1059, 1930.

anterior portion of what is probably the fourth rib on the left side." From this statement, it is presumed that the last mentioned tumor was of osseous origin and extended to involve the tissues about the left breast.

*Size of Tumor.*—In 4 instances the size of the growth was not stated. In the other 6 cases, the surgeons described these growths as to size in the following terms: a man's fist; an egg; 9 by 8 by 8 cm.; the size of a ham, and in 2 instances the size of an orange.

*Rate of Growth.*—The myeloma was stated to have developed rapidly in the two months prior to operation; in case 5499, the growth was a slow-growing tumor, but attention must be called to the statement that the tumor was subjected to roentgen therapy over its known duration of two years; in 1 instance, in which the tumor had been present for three years, it had grown more rapidly during the last three or four months, and at the time of operation was the size of a ham and fixed to the thoracic wall. No statement was given concerning the rate of growth in seven instances.

*Discharge from Nipple and Ulceration.*—If in any case there was discharge from the nipple or ulceration of the surface skin, this was not stated. Ulceration was not recorded on inspection of the specimens at the laboratory.

*Involvement of Muscles.*—With the exception of an instance in which extension went through the muscles and fixed the growth to the wall of the chest, no mention of invasion of the muscles was made in the clinical data on these cases while in the laboratory it was found histologically in 2 other instances. Muscle is known, then, to have been involved in 3 cases.

*Metastasis to Axilla or Other Tissues.*—In 7 instances, there was no information relative to metastasis or involvement of other tissues or organs. One case showed extension to the axilla. In the case of myeloma it was stated that the fourth rib on the corresponding side showed an apparent growth (which possibly was the primary tumor), and that the patient died presumably as the result of metastasis to the spine. Several months after the tumor and breast had been removed, one patient had metastases to the lungs.

*Previous Treatment.*—In case 5499, it was stated that the tumor had been given roentgen treatments throughout the period of its known duration, two years. In no other case was there a record of previous treatment.

*Clinical Diagnosis.*—Clinical diagnoses as submitted for the various specimens were: not stated, 1 case; questionable, 2; fibroma, 1 (the leiomyosarcoma); tumor, 1; cancer, 1; fibrosarcoma, 1; sarcoma, 2,

and carcinoma, 1 (the myeloma). In one half of the cases the clinical diagnosis of a malignant tumor was made, and the growth was definitely considered as a sarcoma in 3 instances.

#### PATHOLOGY OF SARCOMA OF THE MALE BREAST

Geist and Wilensky<sup>20</sup> tabulated 19 types of sarcoma of the breast, and they further included a column headed "unclassified." Although it may appear desirable to some to have such types as cystosarcoma, cystoid sarcoma, plexiform sarcoma, perithelioma, angiosarcoma, polymorphous cell sarcoma, adenosarcoma, alveolar sarcoma and cystosarcoma phylloides, I can see no advantage in such an unwieldy classification. In fact, I question the use of such terms as adeno, alveolar, cysto and cystoid when used in the diagnosis of sarcomas. They are terms that belong with structures in which there are epithelial elements, while perithelioma is used for a hemangio-endothelioma perivascular, as seen in a perithelial organ, which is a tumor that should be distinguished from the sarcomas. The classification herein used is based on a restricted use of the term sarcoma as limited to the atypical histioid neoplasms.

In the group of sarcomas here presented there was nothing outstanding individually or collectively, except that the fibrosarcomas constituted one half of the cases, and that there are recorded a case of leiomyosarcoma, one of liposarcoma and one of myeloma. The latter 3 are unusual types, but conform histologically to the lesions of the same class seen in other locations. The spindle cell type is the most common sarcoma of the breast in both sexes. Various authors record this type as being found in from 31<sup>20</sup> to 68 per cent<sup>21</sup> of the cases of sarcoma.

The leiomyosarcoma (case 5499), diagnosed histologically by Dr. Burton T. Simpson, Buffalo, showed all the characteristics of that tumor with its intertwining muscle fibers and a scant stroma of fibrous tissue. The cells were very embryonic in appearance and irregular in their relationship, and mitotic cells were present.

In the case of liposarcoma (case 20317W), which was diagnosed by me, the tumor was centered at about the lower margin of the areolar tissue and extended up and behind the breast, being apparently a growth that arose in the retromammary fat. It was roughly oval, 8 cm. in diameter, irregular in outline, somewhat firmer than normal adipose tissue and of a definite yellowish color. Histologically, it was composed

20. Geist, S. H., and Wilensky, A. O.: Sarcoma of the Breast, *Ann. Surg.* 62:11, 1915.

21. Gross, S. W.: Sarcoma of the Female Breast Based Upon a Study of One Hundred and Fifty-Six Cases, *Am. J. M. Sc.* 94:17, 1887.

of mixed cell elements of varying sizes (fig. 13), some small and some very large, and of varying degrees of granularity, and most of the cells contained fat droplets and globules. Many of the larger cells had heavily stained, irregular-shaped, moth-eaten-appearing, hyperchromatic, large nuclei that often appeared granular, as if undergoing karyorrhexis. The cellular cytoplasm as a whole was acidophilic in staining. Many

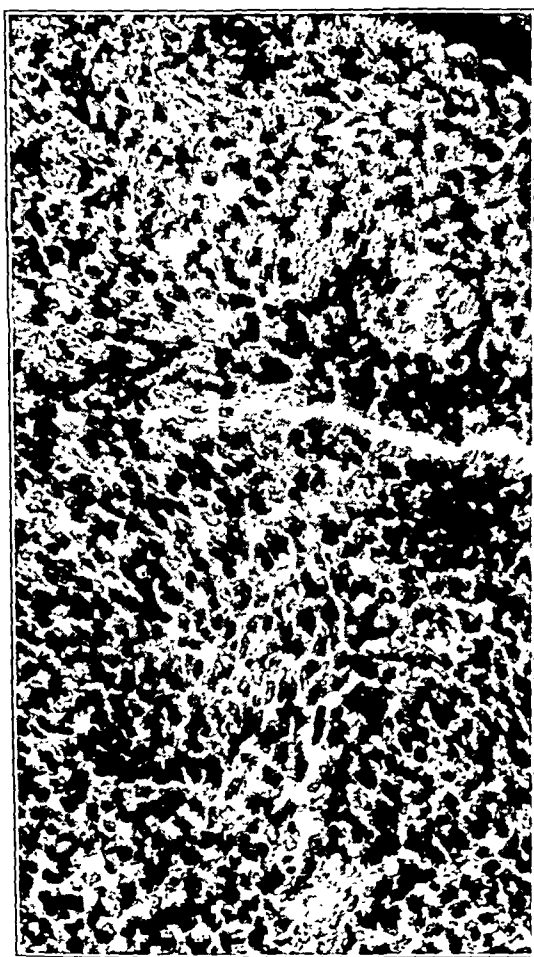


Fig. 11 (case 99936).—Fibrosarcoma.

of the cells contained single globules of fat, and these displaced the cytoplasm and nucleus to one side of the cell. Others contained multiple fat inclusions or droplets (fig. 14), small or large, and in some of these cells, the nuclei appeared displaced, while in others they did not. The shapes as well as the sizes of the cells were variable. They were truly polymorphous cells, including round, oval, polyhedral, elongated and bizarre forms. The outstanding features were the bizarre and



polymorphous cells, the irregularity in their sizes, the marked nuclear variabilities and the cell fat content. Mitotic cells were present in small numbers.

Leiomyoma of the nipple, though rare, has been reported by Virchow and by others,<sup>4f</sup> and myoma of the breast has also been recorded.<sup>1</sup> Since lipomas and leiomyomas of the breast have been recorded, it is not remarkable to find their malignant prototypes—the sarcomas—in



Fig. 12 (case 98579).—Myeloma (myeloid sarcoma).

the same organ. It is difficult to realize that no case of mammary liposarcoma was found recorded in the literature. Mitterstiller<sup>22</sup> in a table recorded a case of leiomyosarcoma in the breast of a man 25 years of age reported by Gibson and Crile in 1914. His only reference to Gibson or to Crile is to an article by Crile in which he stated:<sup>23</sup> "In

22. Mitterstiller, Sepp: Ein Fall von Mammasarkom beim Mann (Mit Bemerkungen zur Frage des Myosarkoms), *Deutsche Ztschr. f. Chir.* **134**:446, 1915.

23. Crile, George W.: A Brief Account of American Surgery During The Past Twelve Months, *Brit. J. Surg.* **1**:505, 1913-1914.

discussion Gibson mentioned 4 personal cases of apparent malignancy, only one of which was cancerous; the others were sarcoma (1) and fibroadenoma (2).” This states nothing about a case of leiomyosarcoma, though the “sarcoma” may have been that form. A search in the *Index Medicus* for the years 1913, 1914 and 1915 and in articles for other references has failed to reveal this specific case report.

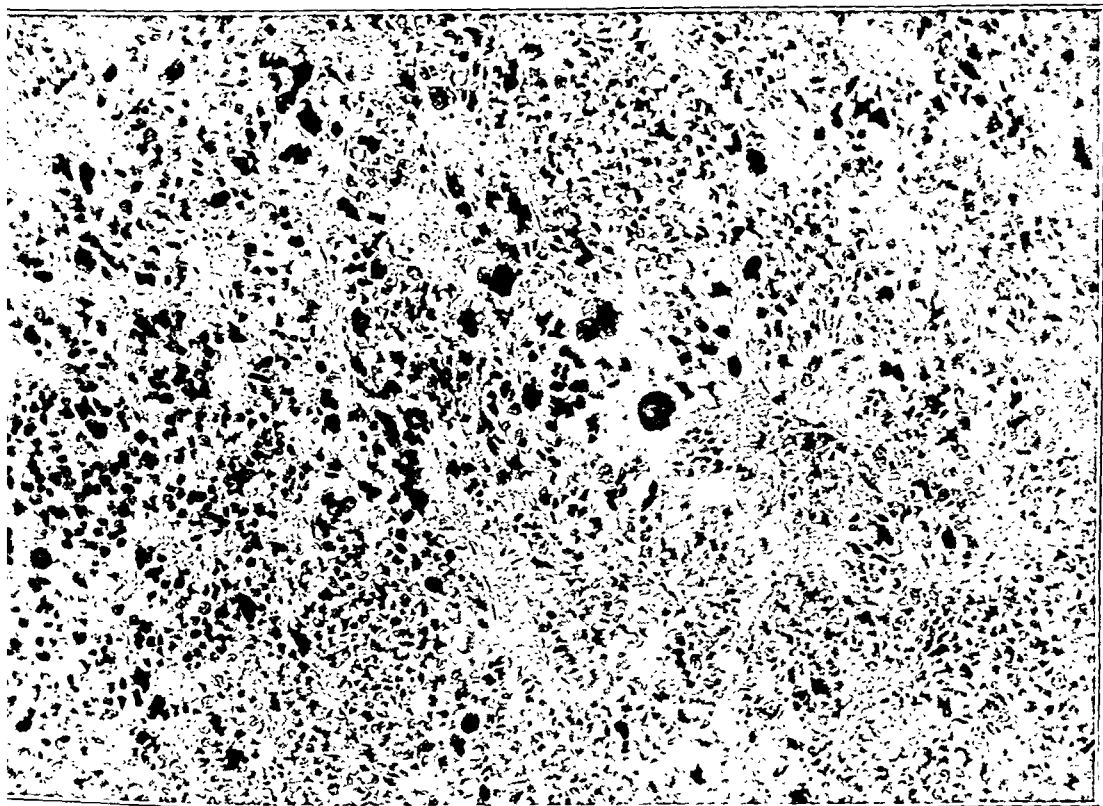


Fig. 13 (case 20317W).—Liposarcoma.

*Myeloma.*—The tumor in case 98579, diagnosed as a myeloma, developed in a man 61 years of age. It was found one year later by his physician, who stated that it was beneath the left breast, apparently attached to the thoracic wall, and involved the anterior portion of what roentgenograms showed to be the left fourth rib. The patient came to the physician with the chief complaint of severe pain in the chest and in the back, undue fatigue and weakness. Studies of the blood revealed a definite secondary type of anemia. Urinalyses showed faint traces of albumin, hyaline, finely and coarsely granular casts and leukocytes. There is no record concerning tests for Bence-Jones proteinuria. An anteroposterior roentgenogram of the chest and a dorsal view of the spine revealed: “Hypertrophic changes (lipping) in lower spine, and the outline of one of the lower

dorsal vertebrae is not quite clean cut. There is no evidence of any disease of the lower ribs." The diagnosis of acute fibrositis and pleurodynia was made. Later examination of the roentgenograms of the chest revealed "An apparent area of destruction involving the left fourth rib anteriorly. While the area is difficult to visualize, it is believed to be a destructive lesion." A number of roentgenologists who have seen these films agree that there was possibly some lesion of the left fourth rib, but none of them would definitely make this diagnosis. The patient died of terminal pneumonia and an apparent involvement of the spine.

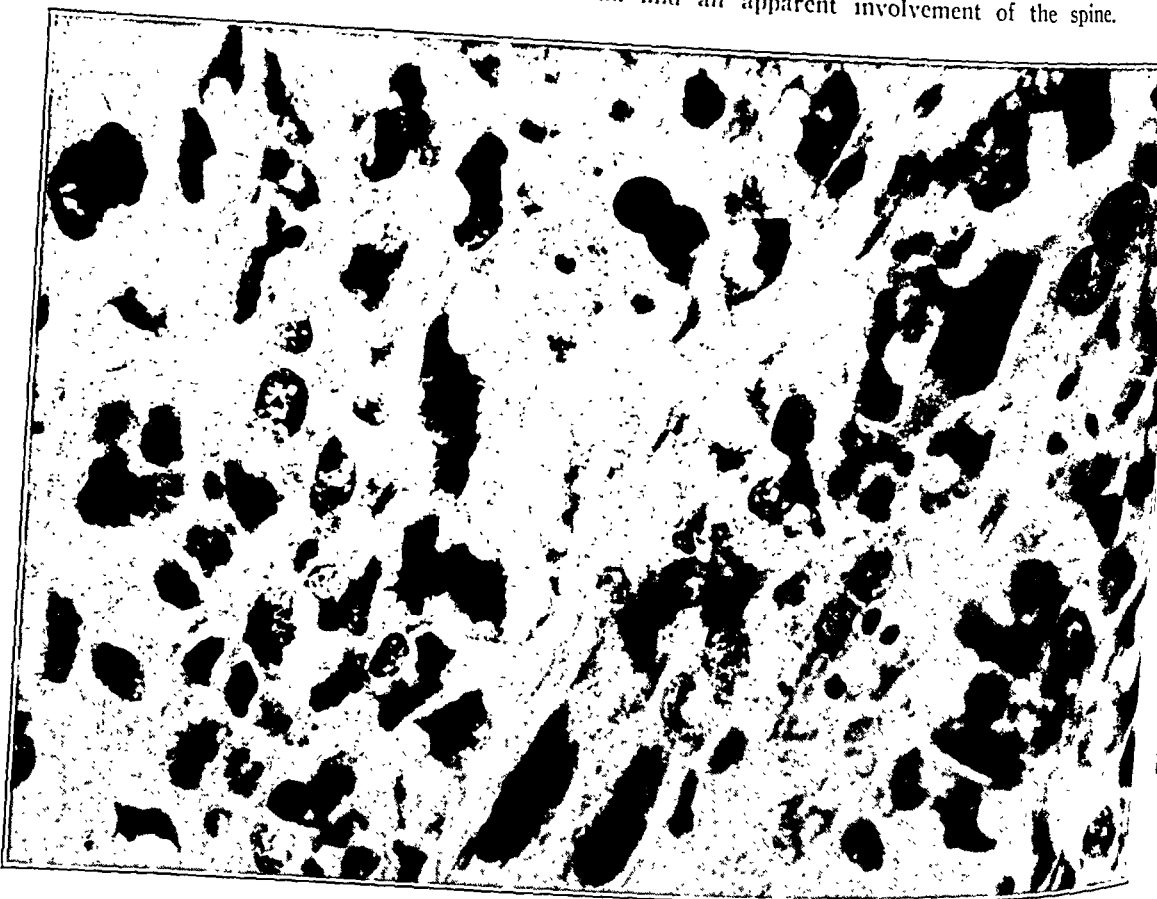


Fig. 14 (case 20317W).—Liposarcoma; high magnification to show cell detail and fat contents.

The tumor mass about the left breast was removed after death. No other autopsy procedure was performed.

Drs. Simpson, Thibaudeau and Burke, of the State Institute for the Study of Malignant Disease, Buffalo, made the diagnosis of a myeloma. Dr. H. R. Brown, of the Genesee Hospital, Rochester, N. Y., later saw the tissue and agreed with that opinion. The tumor, which is said to have been the size of an egg, gave a histologic picture that at once suggested bone marrow (fig. 12), and further studies made this even more impressive. The cells varied much in size, shape and staining reaction. By far the predominant cell resembled the plasmacyte, though there were many large and myeloid types that had large hyperchromatic nuclei. Mitotic cells were present, but in small numbers. Some of the large forms were multinucleated, and nucleoli were visible in a few. The tissue

was of a loose structure like bone marrow, with very scant stroma in which appeared vascular channels of thin walls.

While it cannot be shown conclusively by the roentgenograms made at the time that this tumor arose from the rib, one cannot but believe that this possibly occurred. It of course must be conceded that there is a remote, though improbable, chance that this tumor arose from an embryonal cell rest, or teratoma, in the base of that breast.

Gross<sup>21</sup> recorded instances of osteoid sarcoma and of giant cell or myeloid sarcoma. Geist and Wilensky<sup>20</sup> listed instances of osteosarcoma, giant cell sarcoma, chondrosarcoma and osteochondrosarcoma. Deaver and McFarland<sup>48</sup> discussed a type of giant cell sarcoma having a relationship so like that of bone-forming tissue that they used the appellation "myeloplaxes" as employed by French writers. It therefore is evident that tumors similar in structure to this myeloma have previously been recorded.

It is believed that the simple forms of sarcoma probably arise from their respective connective tissue types normally found in the breast. The complex or mixed types, such as the chondromyxosarcoma, may also arise from these simple connective tissue types and, through metaplasia, take on the histologic features of several types of connective tissue, but it is more probable that they arise as embryonal cell displacements, similar to teratomas elsewhere, and become malignant under the conditions that cause such a change in other teratomatous growths.

*Mitotic Cells in Sarcomas.*—In 3 of the fibrosarcomas and in the lymphosarcoma were found many mitotic cells. In the leiomyosarcoma, the chondromyxosarcoma, the liposarcoma, 2 fibrosarcomas and the myeloma, there were few mitoses. The high number of mitotic cells in the fibrosarcomas accounts to a great extent for the degree of malignancy observed in these tumors of the breast.

*Lymphocytic Infiltration.*—The absence of lymphocytic infiltration about or in sarcomas is a distinctive difference between these tumors and the carcinomas. This statement has no reference, of course, to the true lymphocytic series of cells that make up the integral growing elements of lymphosarcoma and of lymphoblastic sarcomas.

*Degree of Malignancy.*—On the basis of histologic observations, embryonic cell appearances, lack of cell differentiation, mitotic cells, hyperchromatic nuclei, peripheral invasive character, vascularity and thinness of vessel walls, this group of sarcomas was evaluated as to malignancy. Those having a high degree of malignancy were: 2 of the fibrosarcomas, the liposarcoma, the lymphosarcoma and the myeloma. The other 5 (3 fibrosarcomas, the leiomyosarcoma and the chondromyxosarcoma) were of a moderate degree of malignancy.

## GENERAL FACTORS

The pathologic variations between the malignant growths of the male and of the female breast are those of degree and ratio of types, and not of kind. The growths of the male breast are indistinguishable from similar tumors more commonly found in the female breast. The only difference noted was the higher incidence of cysts in those of women. Tumors of the adult male breast should be more easily and earlier recognized than those occurring in women because of the difference in the natural size of the organ, the difference in the amount of the fat bed and the fact that any defect of the male breast should call for investigation. In the case of the female breast there is a natural tendency to procrastinate. The familiarity with repetition of local disturbances causes a woman to become less concerned with this organ, which shows changes incident to physiologic development and function, congestion, response to sex stimulations, hypertrophy, hyperplasia, involution, lactation, infection and other conditions.

The reasons for the generally considered higher mortality from malignant growths of the male breast as compared to those of the female breast appear to be: (1) the higher degree of malignancy as revealed in histologic studies and a greater reversion to less differentiated cells; (2) early invasion of the surrounding tissue, muscle and skin, with ulceration of the latter; (3) lack of the prominent fat bed to aid in limitation of the periphery of the growth, and (4) probably a greater delay in seeking aid.

## THE CHANGING STATISTICS

In the development of the modern operating group, in the program of standardization of hospitals, in the campaigns against cancer and as a source for dependable, proved statistics concerning diseases, cancer in particular, no person stands out so conspicuously as does the surgical and necropsy pathologist. If he has delivered his wares and proved his worth, much of the general credit is due to the members of the American College of Surgeons in their program of standardized requirements. Not many years ago if a specimen removed in the operating room was very suggestive of cancer, it probably reached the laboratory eventually for the opinion of a pathologist who was the handy man for the laboratory, and not a specialized diagnostician of tissue. In many hospitals if the lesions were not particularly suggestive, or the patient was not one of great personal interest, the specimen was discarded or at least rarely, if ever, examined. It is with shame that one must admit that such conditions exist even now in a large number of small hospitals, and even in some of larger size. A study of table 2, which shows the relative frequency of mammary neoplasms in my group and

in that reported by Williams in 1892, should convince one of the truth of the foregoing statements. It will be noted that there is a marked difference in the percentage of cancers, and a still more marked difference between the number and percentage of nonmalignant neoplasms, found then and now.

The American College of Surgeons requires of a class A hospital that it have a well equipped laboratory, the director of which shall be a graduate in medicine and shall have specialized in pathology, and that all tissues removed in the operating rooms shall be submitted to a pathologist for examination and diagnosis. Statistics based on the old system, in which an occasional surgical specimen was submitted to a pathologist and in which autopsies were few, certainly are of little value; in fact, they are misleading when compared with statistics based on the present diagnostic procedures and the high percentage of autopsies. The American College of Surgeons has in the standardization program furthered and aided in establishing the best diagnostic service that the medical profession has yet known, and as a result is giving the sick better service and the scientific world more dependable facts on which statistics may be based.

#### SUMMARY

1. A survey of male breasts is recorded from 117,016 surgical specimens, in which:
  - (a) There were 9,279 specimens, or 7.9 per cent, from the breast in both sexes.
  - (b) There were 308 specimens, or 0.26 per cent, from the male breast.
2. Of the 9,279 specimens, 308, or 3.31 per cent, were from the male breast, which gives a ratio of 1 male to 29.03 female breasts.
3. Of the 308 lesions of the male breast:
  - (a) In 143, or 46.42 per cent, the condition was a nonneoplastic disease.
  - (b) In 165, or 53.63 per cent, there were neoplasms, classified as follows:
    - (A) Malignant growths, 60 cases, or 19.48 per cent.
      - (1) Carcinomas, 50, or 16.23 per cent.
        - (a) Of skin or outer duct origin, 8, or 2.55 per cent.
        - (b) Of duct or acinus origin, 42, or 13.63 per cent.
      - (2) Sarcomas, 10, or 3.25 per cent.
    - (B) Benign growths, 105, or 34.09 per cent.

4. The 165 neoplastic growths were classified as follows:
  - (a) Malignant tumors, 60, or 36.36 per cent.
    - (A) Carcinomas, 50, or 30.3 per cent.
    - (B) Sarcomas, 10, or 6.06 per cent.
  - (b) Benign tumors, 105, or 63.6 per cent.
5. The 60 malignant tumors were classified as follows:
  - (a) Sarcomas, 10, or 16.66 per cent.
  - (b) Carcinomas, 50, or 83.33 per cent.
6. The 50 carcinomas were classified as follows:
  - (a) Growths of skin origin, 8, or 16 per cent.
  - (b) Growths of duct or acinus origin, 42, or 84 per cent.
7. There are recorded a case of liposarcoma, a case of myeloma and a case of leiomyosarcoma in the male breast.
8. There is recorded a case of tuberculosis and scirrhous carcinoma in the male breast.
9. There is reported a case of carcinoma of the male breast with extreme generalized carcinomatosis at death, including metastases to the suprarenals, in which the skin showed the pigmentation seen in destructive lesions of the suprarenals.

#### CONCLUSIONS

1. The most frequent lesions of the male breast are the non-neoplastic processes (46.42 per cent).
2. The second most frequent lesions of the male breast are the benign tumors (34.09 per cent).
3. The third most frequent lesions of the male breast are the carcinomas (16.23 per cent); tumors of skin origin account for 16 per cent of these, and those of duct or acinus origin account for 84 per cent.
4. Sarcomas constitute 3.25 per cent of the lesions of the male breast.
5. Carcinomas of the male breast were responsible for 1.24 per cent of the carcinomas of the breast in both sexes.
6. Of the sarcomas of the breast in both sexes 19.61 per cent were found in the male breast.
7. Carcinomas are 80 times proportionately more prevalent in the female breast than in the male.
8. Sarcomas are 16 times proportionately more prevalent in the male breast than in the female.

9. Carcinomas occur in the male breast only 5 times more frequently than do sarcomas, whereas in the female breast carcinomas are seen 79 times more often than are sarcomas.

10. Of all the lesions of the breast, 3.31 per cent occurred in men.

11. The average age of patients at the time of observation for carcinoma was 57.7 years, and for sarcoma, 39.7 years.

12. The present day standardization of hospitals and laboratories is promoting a better and more extensive diagnosis of tissues and more dependable records from which statistics may be compiled.

Dr. Burton T. Simpson, Director, and the members of his staff at the State Institute for the Study of Malignant Disease, Buffalo, permitted the free use of their materials and records. Dr. Frank G. Nifong, Columbia, Mo., provided the history and data on case 25-20M.



# SURGERY OF THE SESAMOID BONES OF THE GREAT TOE

AN ANATOMIC AND CLINICAL STUDY, WITH A REPORT OF  
FORTY-ONE CASES

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During the past twenty years there have appeared in the literature numerous papers relating to the sesamoid bones of the great toe and their clinical significance. One is impressed, in reading most of these articles, by the uncertainty regarding the embryology, anatomy and function of these small structures, and by the number of disputed points relative to their surgical pathology and treatment. In view of this uncertainty, and because no thorough survey of the literature has appeared, we report this study made in connection with the follow-up investigation of our own cases. Our plan is to review the literature, to cite the results of our own anatomic and pathologic studies and finally to report a series of cases in which sesamoidectomy was performed for the relief of pain.

## HISTORICAL SUMMARY

Not always have the sesamoid bones of the great toe played a rôle of such relative insignificance as they play today. The medial sesamoid has been identified by many as being the bone "Luz," a mythical bone believed in medieval times to be the indestructible seed from which the body would be resurrected on the Day of Judgment. To quote Caspar Bauhinus:

Hebrew writers affirm that there is a bone in the human body . . . which cannot be destroyed by fire, water or any other element, nor be broken or bruised by any force; this bone God shall, in His exceeding wisdom, water with the celestial dew, whence the other members shall be joined to it, coalescing to form the body, which, breathed upon by the Divine Spirit, shall be raised up alive.

The idea of the bone "Luz" is said to have originated with one Rabbi Uschaia, in the third century, A.D., and through the Middle Ages various philosophers and mystics identified it with various bones, such as the os sacrum, the "eighteenth vertebra," the coccyx and the medial

sesamoid bone. Garrison expressed the belief that the last-named bone corresponds most closely with the descriptions of the "Luz." Vesalius, in his chapter on the sesamoid bones, said that this myth was given credence only by the magicians and followers of occult philosophy, and gave his own opinion of it in these words of a true scientist:

But the dogma which asserts that man will be regenerated from this bone, of which we have just narrated the immense fiction, may be left for elucidation to those philosophers who reserve to themselves alone the right to free discussion and pronouncement upon the resurrection and immortality of the soul.<sup>1</sup>

Since the time of Vesalius and Leonardo, the sesamoid bones have played a less spectacular, if no less useful, part in the human economy.

The term "sesamoid" denotes the similarity between the shape of these bones and that of the flat, oval seeds of the *sesamum indicum*, an ancient East Indian plant used by the Greek physicians for purging. The name is said to have been applied to the bones by Galen.

In 1736, Robert Nesbitt, of London, showed that the sesamoid bones are present beneath the first metatarsal head at the third month of fetal life. In spite of this, certain French writers, such as Boyer (1803) and Gillette (1872), as well as John Bell of Edinburgh, held that sesamoid structures were not present in fetus or child, but were the result of constant trauma to tendons in standing and walking. In 1892 appeared the exhaustive monograph of W. Pfitzner on the human sesamoid bones and their variations, in which the findings of Nesbitt were definitely confirmed. Since that time other workers have made similar observations; there remain, however, differences of opinion as to the exact place in which the sesamoid anlagen appear. Quain held that they formed in the tendons of the flexor brevis hallucis; Nesbitt and Pfitzner believed that, as in the case of the patella, the sesamoids appear first in the joint capsules, being later invested by the fibers of the overlying tendons. Bradley, from observations on pig embryos, claimed that the sesamoids are cartilaginous buds separating off from the joint side of the phalanx, just beneath the flexor tendon.

The constant presence of the sesamoid bones and the variations in their structure were further demonstrated after the introduction of the roentgen rays. In 1901, Schunke published the first description of a human sesamoid bone transversely divided into two parts, which, because of a history of injury in the patient, he called a fracture and "cured" by immobilization of the foot. In 1904 operative removal of one of these ossicles for the relief of pain was first described. The true origin of the line of partition often seen in sesamoids was described by Momburg (1907) and by Igelstein (1908), but these lines of developmental division are still often referred to as fractures, although most authors are

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1. Garrison's translation.

aware that the anomaly is of frequent occurrence. Several authors have recently examined series of roentgenograms of relatively normal feet, and have made varying reports as to the incidence of divided sesamoids; Geist found 16 per cent in a series of a hundred feet, Bizarro 4 per cent, and Freiberg the surprisingly low incidence of one division in a series of a thousand feet.

In recent years, especially among French, German and South American writers, considerable attention has been paid to the pathology and treatment of painful sesamoids in which there was no division and hence no question of fracture. Trèves, Schütz, Finochietto, Köhler and others have described a condition in which there is intrinsic pain, and which is characterized in the roentgenograms by a stippled, spotted appearance instead of the smooth even texture of normal spongy bone. These authors have described the same lesion under different names, and this has resulted in a confused reduplication of terms, viz., "typical disease of the sesamoid bones," "sesamoiditis," "osteochondritis," "osteomalacia," "osteitis fibrosa," "juvenile necrotic osteopathy," "Köhler's" or "Schlatter's" disease of the sesamoids and, more recently, "sesamoid insufficiency" (Wisbrun). Trèves did not mention any microscopic sections, but Schütz, Renander and Wisbrun described "necroses" in the trabeculae and marrow of the bones. Finochietto spoke of a softening of the bone and the velvety appearance of the articular cartilage. Schütz said that this condition is found only in congenitally divided sesamoids, and that the division plays a still unknown part in its development. Finochietto gave an extensive differential diagnosis between "sesamoiditis" and "arthritis deformans" of these bones, one of the differential points being the stippled or "leopard-skin" appearance of the bone in the roentgenogram in the former condition. This author gave a good description of the symptoms and signs of painful sesamoid bones, and concluded that, since the line of division in bipartite sesamoids is a failure of fusion between two centers of ossification, it is comparable to any epiphysis, and that therefore "sesamoiditis" is an osteochondropathy exactly like those occurring in other epiphyses and apophyses, such as Schlatter's disease of the tibial tubercle.

One author (Lange) has described a case of "sesamoiditis" proceeding to suppuration; this was apparently an embolic suppurative osteomyelitis.

The recent literature seems still to be mostly concerned with the question of fractures in these bones. Various reasons are given for making this diagnosis rather than that of developmental division. Hobart reported a case involving the lateral sesamoid, giving as one reason for calling it a fracture the fact that no congenital division of the lateral sesamoid had been described. In a subsequent paper, however, he reported finding three such anomalies in the German literature. Scott.

in an excellent article on the congenital variations of the sesamoids, corrected the impression then current in the British literature, that partition always indicated fracture; he drew attention to the possible forensic importance of this diagnosis, and showed that roughness of the opposing surfaces in a divided sesamoid is not necessarily evidence of fracture. He found the anomaly to be always bilateral in those of his cases in which roentgenograms were made of both feet.

Stumme, Preiser and Morian claimed to have produced experimental fractures of these bones in cadavers by indirect and by direct violence. Skillern attempted the same procedure on the thumb, by clamping the metacarpal bone in a vise and then striking the distal phalanx of the thumb with a mallet, forcing it into marked hyperextension. All these authors reported success in fracturing the bones, but it should be noted that none of them demonstrated by a pre-experiment roentgenogram the absence of developmental divisions in the bones on which they were working. Skillern reported fractures in 18 per cent of his cases, and said that in several of his experiments the sesamoids remained intact even though fractures of the metacarpal or phalanx occurred. This is significant. This author gave no figures for the frequency of congenital division of the sesamoids at the thumb.

Bizarro has contributed two papers to the subject, the first of which is an admirable presentation of the comparative anatomy and physiology of the sesamoid and supernumerary bones of the foot. He showed that most mammals have sesamoid bones in positions analogous to those in the human skeleton, the size and habits of the animal having no constant relation to the size of the sesamoids. Unlike the supernumerary bones of the foot, these ossicles are not residuals of primitive tarsal bones, but are persistent sesamoid structures throughout the mammalian family; the tarsal supernumerary bones have a well defined phylogenetic meaning, the sesamoids an unknown anatomic pedigree. As to the reason for the appearance of these bones and the variation in their structure, Bizarro concluded:

Phylogeny and function combined appear to be the two causes of sesamoid formation and development, the former as it were planting the seeds for their formation and the latter acting daily and with every movement, promoting the increase in size of these structures. It is hardly possible to accept either of these theories separately, and the only obscurity remaining lies within the elastic boundaries indicated by the term "phylogeny."

Bizarro, in his second paper, dealt with the traumatology of the sesamoid bones, and reported a case of a third sesamoid, lying between the two constant bones, called by the author "*os intersesamoideum*."

Wood-Jones stated that in the rabbit the two great toe sesamoids are united by a narrow bony isthmus, thus forming one dumb-bell shaped bone.

Robinson accused the great toe sesamoids of being the sole cause of hallux valgus and bunions, alleging that they first become enlarged, then dislocated into the intermetatarsal space, forcing the first metatarsal head medially. He stated that the degree of hallux valgus is directly proportional to the size of the luxated sesamoid. There is no indication in the literature of this theory having been taken seriously (fig. 15 *A*).

Burman and Lapidus reviewed the literature on the functional disturbances of these bones and of the supernumerary bones of the foot, but they reported no sesamoid cases of their own. They made the apt observation that, as in other fractures, callus will unite the fragments of a fractured sesamoid. This is a definite criterion in the differential diagnosis from developmental division, and we shall refer to it later. In examining roentgenograms of one thousand feet these authors found division of the medial sesamoid in 7.2 per cent, and of the lateral sesamoid in 0.6 per cent.

Geschickter and Copeland, in their recent book, described tumors arising from the sesamoid bones and areas of potential sesamoid formation. These xanthoma variants of the giant cell tumor, formerly thought to arise from tendon sheaths, are slowly growing, rarely metastasizing tumors, having slight tendency to spread or recur locally and sometimes attaining the size of an egg. Cure is usually effected by complete excision of the tumor.

As to the treatment of diseases of the sesamoid bones, opinions again differ. Some authors frankly advocate "conservative" treatment in all cases; others make the reservation that if this fails, surgical excision of the affected bone should be done; still others advocate excision in cases of "sesamoiditis," but splinting of fractured sesamoids. Wisbrun recommended deep roentgen therapy if an operation is declined by the patient. Kellogg Speed held that, if excision is to be performed, both sesamoids should always be removed, since leaving one of these bones in place would cause an unfavorable mechanical situation and subsequent symptoms. The forms of conservative treatment recommended vary from the use of a simple metatarsal pad or bar to the immobilization of the foot and leg in plaster for six weeks. The patients treated conservatively have often been reported as coming to operation later. Results of surgical removal seem to have been uniformly good, except in those cases in which the condition is complicated by serious deformities of the foot, especially clawfoot. Delchef reported three such cases.

#### ANATOMIC STUDIES

In the human adult there are constantly present two osseous sesamoid bones at the metatarsophalangeal joint of the great toe; each is enclosed around the margin of its superior articular facet by the capsule of the

joint and invested throughout the remainder of its surface by the corresponding tendon of the flexor brevis hallucis. These tendons are inserted into the proximal end of the first phalanx of the great toe, and are the only effective plantar flexors of the metatarsophalangeal joint; their fibers bite into the roughened nonarticular surface of the sesamoids, there being no smooth periosteum; hence the difficulty in shelling these bones out of their tendons. The sesamoids articulate with, and rest under, the first metatarsal head, the cartilage of the latter being prolonged proximally for this purpose. From above and in profile they have a characteristic, smooth shape (fig. 1). Though joined together by strong bands of the joint capsule, they are separated from each other by the tendon of the flexor longus hallucis on its way to insertion into the distal phalanx of the toe, and their corresponding articular facets on the metatarsal head are separated by a bony ridge; this ridge is not high



Fig. 1.—Sesamoid bones normal in shape, size and position, shown in anteroposterior, frontal and lateral views.

enough to prevent dislocation of the medial sesamoid laterally in severe hallux valgus. Between the sesamoids and the skin there is normally only the thick fibrous pad of the "ball" of the foot, through which the two small bones may sometimes be palpated. Not infrequently a bursa is interposed between the sesamoids and the skin surface.

We have studied the development of these bones in the human fetus in specimens ranging in age from 8 weeks to 9 months. We were unable to obtain a specimen earlier than the eighth week. Even at this early period, both sesamoid bones are recognizable as islands of undifferentiated connective tissue in their normal location beneath the first metatarsal head. At the tenth week this connective tissue can be recognized as precartilaginous, and at the twelfth there is a definite center of chondrification. These changes occur simultaneously in sesamoids, phalanges and metatarsals. The connective tissue in which the sesamoids develop is seen to be continuous with the periosteum of the

metatarsal proximally and with that of the phalanx distally; by the third month this can be identified as joint capsule, and the fibers of the tendon invest the lower portion of the bone between the third and the fourth months. By the fifth month these bones have their normal adult shape, and the development from then on is only in size. At no time did we see any evidence of their arising as cartilaginous buds from the phalanx (fig. 5).

The sesamoids normally begin to ossify at about the eighth year, and as a rule appear completely ossified by the eleventh. Variations in this rule, of course, occur, Nesbitt having described a center of ossifica-



Fig. 2.—Sesamoids present at all metatarsal heads, a total of seven in each foot. Luxation of the left lateral sesamoid is seen.

tion in a sesamoid of an infant. In our series we found no case in which the bones were visible in the roentgenogram earlier than the eighth year. Their ossification may be very irregular. There may be one, two or more centers of ossification, and the multiple centers may or may not fuse later. Their failure to fuse is believed to give rise to the bipartite or multipartite appearance in the roentgenogram. There is no longer any serious doubt as to the frequent occurrence of these developmental variations; it is certain that they exist in persons who have had no known injury, and that such persons may lead a long and active life without any symptoms referable to the sesamoids.

In order to determine the incidence of these anomalies and the relative frequency of the various types of division, we reviewed a series of 1,025 consecutive roentgenograms of feet in our dispensary, regardless of diagnosis. All were of patients above 10 years of age. One hundred and ten feet, or 10.7 per cent of those examined, presented an unquestionably divided sesamoid bone. Six feet showed division of the lateral sesamoid and three of the lateral only. Roentgenograms of both feet were available in eighty-three of the hundred and ten cases; in these the anomaly was found to be unilateral in 75 per cent and bilateral in 25 per cent. Of the bilateral cases, 85 per cent showed symmetrical

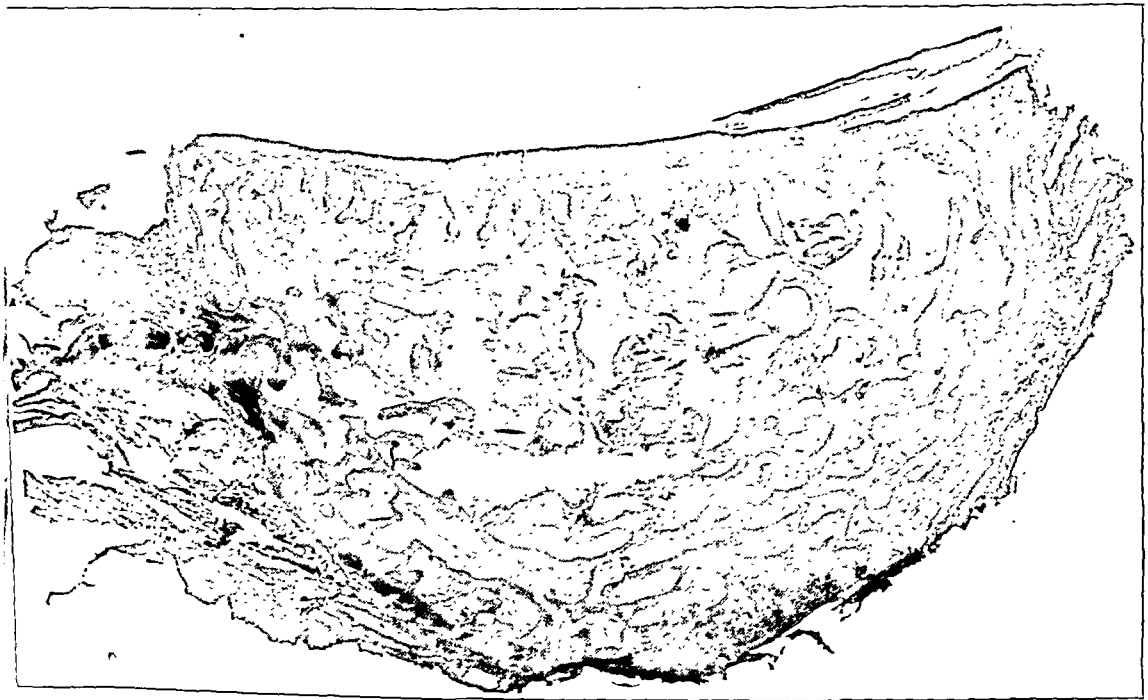


Fig. 3.—Low-power view of a sagittal section of a normal sesamoid. Trauma at operation has damaged the articular cartilage.

division, i. e., had the same type of division in the corresponding bone of each foot. It is thus seen that unilaterality cannot be trusted as a criterion of fracture in these bones.

Of the divided sesamoids in this series, eight showed characteristics considered by some writers as indicative of fracture: the lesion was unilateral, the opposed edges of the two "fragments" were rough and serrated, and there was relatively wide separation of the segments. On inquiry into the history of these patients it was found that none of them had come to the dispensary because of sesamoid pain, and that none had knowingly had an injury sufficient to fracture one of these bones.



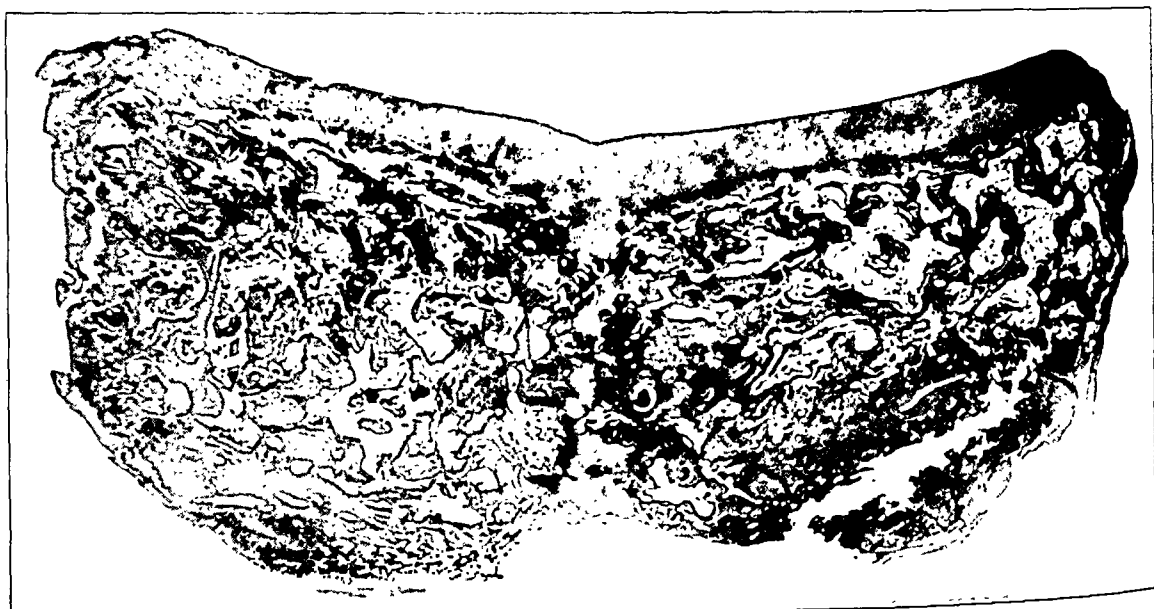


Fig. 4.—Similar section of a bipartite sesamoid. Note cartilage extending downward between the two segments. The bone was damaged in removal.

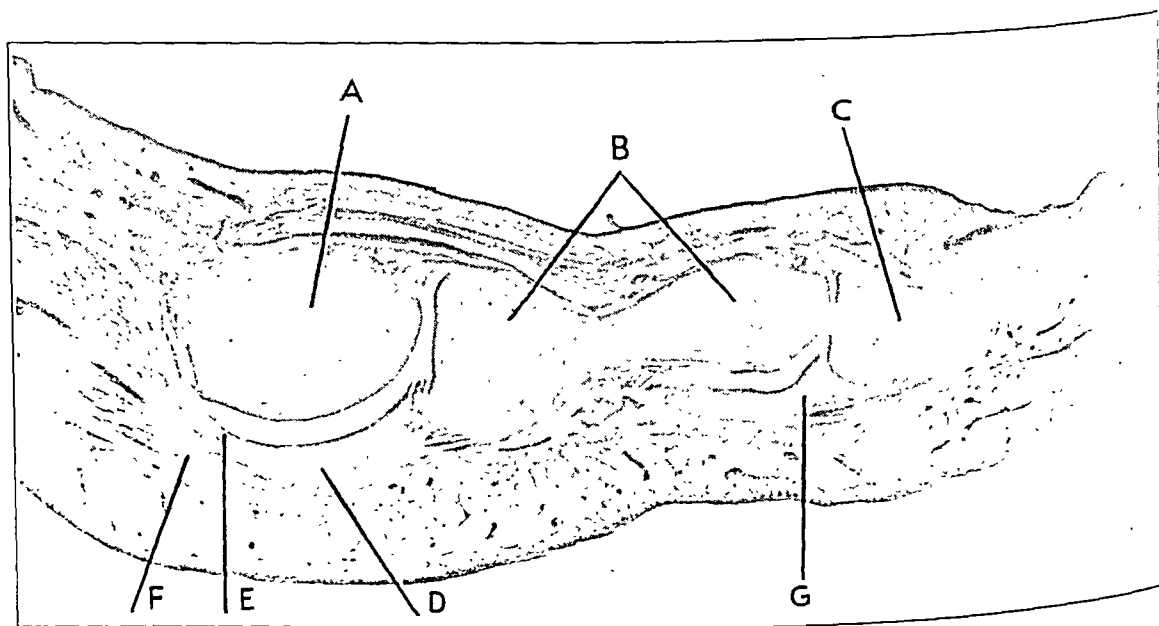


Fig. 5.—Low power view of a sagittal section of the great toe of a 5 months fetus: *A*, metatarsal head; *B*, proximal phalanx; *C*, distal phalanx; *D*, medial sesamoid bone; *E*, joint capsule; *F*, flexor brevis hallucis tendon; *G*, flexor longus hallucis tendon.

The presence or absence of other anomalies in the foot, such as supernumerary bones of the tarsus, is sometimes used as evidence that a division of the sesamoids is due to fracture. To determine whether or not these anomalies are present more frequently with divided sesamoids than with undivided ones, bilateral anteroposterior and lateral roentgenograms of the feet of two hundred and nineteen patients over 10 years of age were examined. In this series, seventy-nine feet had divided sesamoids and three hundred and fifty-nine had no divisions. Anomalies examined for were: a completely separate os tibiale externum, os peroneum, os trigonum and os intermetatarsium. Other anomalies were occasionally seen, but not often enough appreciably to affect the percentages. The study showed that 32 per cent of the feet with divided sesamoids presented other anomalies in the same



Fig. 6.—Developmental division of a medial sesamoid.

foot, whereas 35 per cent of those without divided sesamoids showed other anomalies. Considering both feet in each patient, it was seen that, of the cases of divided sesamoids, 67 per cent showed some other anomaly in the same or the opposite foot, as compared with 51 per cent in the group without divisions. Obviously, these figures are so similar that this criterion is not reliable in making the differential diagnosis of fracture of a sesamoid.

Considerable variety was shown in the shape and size of the segments of the divided sesamoids as shown in the roentgenograms. In the anteroposterior view the most frequent types of division, in the order of their incidence, were as shown in figure 16. The more or less regular segments shown there are often distorted by arthritic deposits. Our cases of sagittal division, as in type 9, figure 16, could be seen only in the frontal view.

The other sesamoid bones of the extremities may show congenital division, those at the thumb especially. Figure 12 shows bipartite sesamoids at the heads of the second and fifth metatarsals. In our files there are roentgenograms of seventeen cases of congenital division of

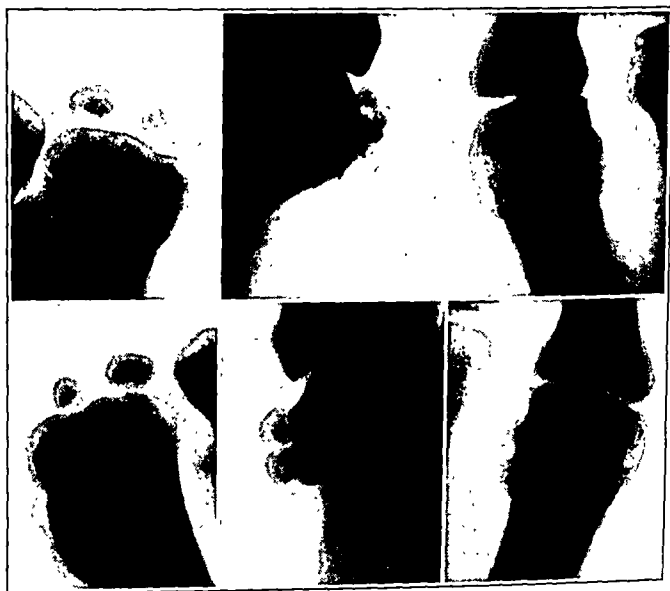


Fig. 7.—Developmental division of both sesamoids at each first metatarsal head in the same patient. There were no symptoms.



Fig. 8.—Right medial sesamoid divided. The left medial sesamoid is elongated, having developed from two centers now united.

the largest of the sesamoids bones, the patella. We have examined roentgenograms of two hundred hands in order to determine the incidence of this anomaly at the thumb. Twelve hands, or 6 per cent, showed definite division, and fifteen more showed a possibly divided sesamoid. In routine films of the hand these bones are not well shown, so that the incidence is undoubtedly greater than 6 per cent, probably

twice that figure. The line of division was usually transverse in the medial, and longitudinal in the lateral, sesamoid. In no hand were both bones found divided. Ossification here is apparently not complete before the fourteenth year, as several patients of 12 and 13 years were found without ossified sesamoids at the thumb.

No definite cause can as yet be assigned to the failure of fusion of the centers of ossification in the sesamoid bones. Analogies to this failure appear in other parts of the body, such as in the posterior ele-



Fig. 9.—Various types of division of the medial sesamoid

ments of the vertebrae and between the tarsal navicular bone and os tibiale externum. Just why the failure of fusion occurs in the medial sesamoid of the great toe so much more frequently than in the lateral is uncertain; the cause may be related to the greater and more frequent trauma undergone by the medial bone because of its location. On the other hand, lines of ossification are greatly influenced by the position of blood vessels, and the latter seem to be quite inconstant in their distribution in these bones. Further work is necessary before this question can be answered definitely.

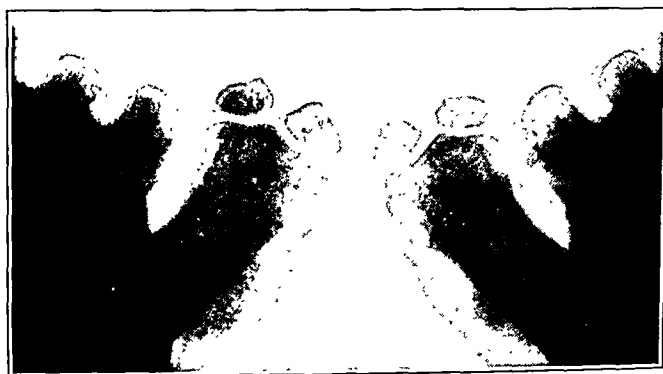


Fig. 14.—Bilateral os intersesamoideum.

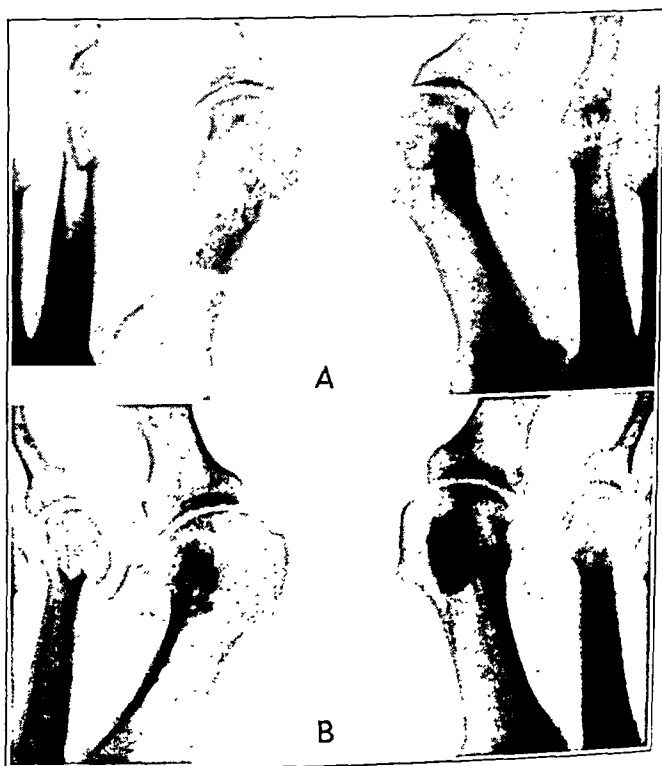


Fig. 15.—*A*, marked hallux valgus, obviously not caused by the small luxated lateral sesamoids. *B*, unilateral subluxation of lateral sesamoid, with pseudarthrosis with second metatarsal head; possibly one cause of sesamoid pain.

Microscopically, our sections of normal sesamoid bones show considerable variation in structure, both as to the number and thickness of the trabeculae and as to the content of the intertrabecular spaces. We have not found any red bone marrow in these spaces, which are usually occupied by loose fatty tissue. Usually the structure of the bone is quite compact (fig. 3), and it often, but not always, shows the appearance described by Wisbrun, with the trabeculae in the upper half running vertically and those in the lower horizontally. Since the greater part of the weight-thrust is through the posterior part of the bones, the trabeculae here are thicker. In the case of the congenitally divided bones, the articular cartilage is seen to dip down between the two segments, an appearance not at all suggestive of fracture (fig. 4). The periosteum is indistinguishable from the investing tendinous fibers, which insert deeply into the rough plantar surface.

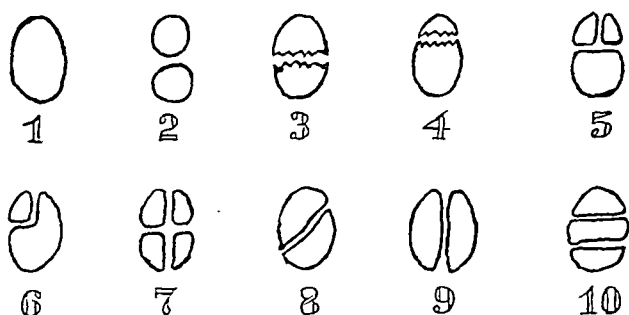


Fig. 16.—Diagram showing various types of developmental division of sesamoid bones in our series of roentgenograms, arranged in the order of their frequency. Number 1 represents a normal sesamoid for comparison. Type 9 could be seen only in our frontal-view roentgenograms.

The function of all sesamoid bones, speaking phylogenetically, is the protection of tendons which glide over the prominent and exposed surfaces of joints. They also act as pulleys to alter the direction and increase the mechanical advantages of the tendons in which they are embedded. That there are no sesamoid bones over such prominent and exposed joints as the knuckles in the human hand may be explained by the fact that until man assumed the upright posture, it was the plantar (now volar) surface of the hand which received most of the trauma and exposure. It is interesting to note in this connection, however, that Retterer has found fibrocartilaginous sesamoids consistently in the dorsal tendons at the first metatarsophalangeal joints of the lion and the cat.

In addition to the aforementioned functions of sesamoid bones in general, those at the great toe serve to protect the flexor longus hallucis tendon which lies between them: also, as was suggested by Hancock in 1873 and brought out more recently by Morton, they serve an important

use in protecting the head of the first metatarsal and lifting the head of this bone off the ground so that it will be level with, or slightly higher than, the outer metatarsal heads.

#### PATHOLOGY

In the records of the New York Orthopaedic Dispensary and Hospital there is only one proved case of fracture of a sesamoid of the great toe. This fact alone, in a large clinic, lends proof to the contention that fracture of these bones is a rare condition. In the case referred to (this case is not included in the series reported here, as the patient was admitted after the study was made), the roentgenogram at the time of injury showed what appeared to be a developmental sagittal division of the lateral sesamoid; several weeks later the roentgenogram showed evidence of a reparative process between the two segments. Conservative treatment having failed to relieve this patient, the bone was excised, and sections showed the presence of callus between the fragments. We believe that it is unjustifiable to make the diagnosis of fracture of a sesamoid without this demonstration, by roentgenogram or section, of subsequent callus formation, or unless there was a previous roentgenogram in which the bone was seen to be undivided. Thus congenital division being so frequent, and simulating fracture so closely in feet known not to have been injured, the burden of proof is on him who makes the diagnosis of fracture.

If the line of division seen in sesamoid bones is due to congenital failure of fusion between two centers of ossification, and these centers tend to fuse, the incidence of divided sesamoid bones would be expected to decrease as age increases; if the line is due to fracture one would expect the opposite, namely, an increase in the incidence as age progresses and the bones become harder and more brittle and the trauma at the metatarsal head becomes greater. That the former of these conditions is true is shown by table 1, which contains an analysis of bilateral roentgenograms of the feet of four hundred and thirty-three patients above the age of 10 years (866 feet). Table 1 shows the number of feet with divided sesamoids in various age groups from 10 to 60 years. It will be seen that the incidence steadily declines after the fifteenth year. The number of bilateral cases is seen to be highest in the earlier age groups. The last two columns of the table demonstrate a fact which is the converse of the aforementioned observation, and that is that the incidence of sesamoids developed in two parts now united (fig. 8) increase as age increases and as divided sesamoids decrease.

With fractures thus practically ruled out, what are the causes of sesamoid pain? In our series of patients operated on several definite pathologic conditions to which the symptoms could be attributed were

found; there were some cases, however, in which no definite lesion could be demonstrated. In the order of their frequency the following lesions were encountered:

(a) Involvement in metatarsophalangeal arthritis, as shown by lipping and spurs on the sesamoids, with consequent enlargement, pitting and thinning of the articular cartilage and sometimes partial or even complete fusion of the bone to the metatarsal head. This may, of course, be present without evidence of arthritis at other joints. The lipping may be visible in the roentgenogram, and fusion to the metatarsal head may be demonstrated by profile views with the toe first in hyperextension and then in plantar flexion. Complete ankylosis of these bones to the metatarsal head results in loss of extension and of active flexion at the metatarsophalangeal joint.

TABLE 1.—*Analysis of Roentgenograms*

Age	Number of Cases	Number of Feet Examined	Number of Feet Showing Divided Sesamoids	Per Cent of Total	Number of Bilateral Cases	Number of Feet Showing Sesamoids Developed in Two Parts, Now United	Per Cent of Total
10.....	45	90	18	20	4	0	0
15.....	49	98	21	21	5	8	2
20.....	45	90	14	15	5	12	3
25.....	41	82	8	10	1	8	2
30.....	51	102	9	9	0	32	8
35.....	50	100	10	10	0	40	10
40.....	44	88	8	9	1	45	12
45.....	56	112	4	5	1	12	3
50.....	33	66	4	6	1	28	7
55.....	24	48	4	8	2	0	0
60+.....	15	30	1	3	0	28	7
Totals.....	433	866	101	..	20	216	..

(b) Chronic or subacute bursitis underlying the sesamoids. These bursae are found more frequently in clawfoot deformities and in badly muscle-bound feet, and are more liable to become inflamed in these types of feet. They vary in size, and the severity of the symptoms is not necessarily directly proportional to the size of the bursa.

(c) Medial luxation of the medial sesamoid following exostectomy for hallux valgus and bunion. In these cases, lateral roentgenograms at rest will show the sesamoid in its normal location, while the standing view shows the medial and upward dislocation.

Enlargement of the sesamoids does not in itself seem to be a cause of pain. The aforementioned patients in whom there were no demonstrable pathologic changes were operated on, as were all the patients in this series, for painful sesamoids unrelieved by conservative measures. The explanation of the pain in these cases is probably the presence of localized arthritis not appreciable in roentgenogram or section, rather than



to pressure on local nerves, as has been suggested by some writers. In bipartite sesamoids the pain may be due to a process similar to Schlatter's apophysitis at the tibial tubercle, but in our series only two of the cases of unexplained pain were in bipartite sesamoids; this contradicts E. Müller's statement that "all painful sesamoids are bipartite."

In our sections we have seen no pathologic picture comparable to that described by Renander, Schütz, Finochietto and others and called "sesamoiditis," "osteomalacia," "osteochondritis," "osteitis fibrosa," etc. We have three roentgenograms, however, which show the stippled appearance described by these authors. Incidentally, these patients have not as yet complained of sesamoid pain. Roentgenologically these lesions have the appearance of a traumatic osteitis, such as is seen in the inflections of the metatarsal heads from repeated small traumas. It is possible that this and the aforementioned obscure conditions are identical, in which case the situation could be cleared considerably by adopting a single and inclusive term. "Traumatic osteitis" expresses the uncertainty that exists and must exist regarding these questionable conditions until further work is done on the pathology of these bones.

#### REPORT OF CASES

In the records of the New York Orthopaedic Dispensary and Hospital there were, up to January, 1930, thirty-one cases in which sesamoidectomy alone had been performed for the relief of sesamoid pain. Of these, ten were bilateral, making a total of forty-one feet operated on. This is exclusive of all those cases in which the sesamoid bones were removed as a prophylactic measure at the time of other operations at the first metatarsal head, and also of those cases in which operations to modify the architecture of the foot were performed at the same time. The success or failure of these other procedures would obviously affect the result of a sesamoidectomy, so that even though the sesamoids were the seat of real pain, these complicated cases were excluded from the present study.

Of the thirty-one patients operated on, twenty-four were female and seven male. The average age at operation was 25 years, and the average duration of symptoms was three years, the longest being twenty years, the shortest two weeks. The average length of time elapsed since the operation was three years and two months, varying between six months and eight years. The onset of symptoms was gradual, without a history of injury, in fifteen cases; it followed other operations on the feet (such as exostectomy for hallux valgus) in five cases; in two the onset was sudden, following injury. Neither of the last two cases showed division of the sesamoids. In nine cases the mode of onset could not be determined. Preoperative roentgenograms were

available for thirty-two of the feet operated on, and of these, two, or 6.2 per cent, showed developmental division of the bone. None showed fractures. Conservative preoperative treatment had been tried in all cases, without complete success. Most of the cases of painful sesamoids in our dispensary are relieved by such conservative measures as a metatarsal pad or bar, massage and antiarthritic treatment, only 40 per cent of the cases coming to operation in the period covered by this report.

Eight of the feet operated on in this series showed varying degrees of clawfoot deformity, seven showed other deformities which might contribute toward sesamoid pain, and twenty-six were relatively normal feet. A mild degree of muscle-bound foot was not considered a deformity.

The operative technic was the same in all cases: exposure of the bones through a mediodorsal or medio-inferior longitudinal incision over the first metatarsophalangeal joint, avoiding surfaces which will bear weight or be rubbed by the shoe; and excision of the bone, by sharp dissection, from the tendon in which it lies. Great care must be taken not to divide the flexor brevis tendon, especially when both bones are removed, and for this reason the use of a tourniquet is essential. The bursa underlying the sesamoids is usually not removed.

In twenty-five feet both sesamoids were removed, in fifteen only the medial, and in one only the lateral. The average number of days in bed after operation was eight; in the hospital, eleven. The only postoperative complication was a superficial wound infection in one case.

In studying the results of the operations, the cases were divided into four groups; these, with the number of cases in each, were as follows:

Group 1. Those in which the patients obtained complete relief of symptoms, with restoration or maintenance of normal function. In this group there were seventeen cases, or 41.5 per cent.

Group 2. Cases which showed improvement but which could not be admitted to group 1 because of minor imperfections in the result, such as tender or keloidal scars, impaired motion at the metatarsophalangeal joint, persistence of mild pain under the metatarsal head, etc. This group comprised twelve cases, or 29.3 per cent.

Group 3. In this group there were placed seven, or 17 per cent, of the patients, whose symptoms were relieved but in whom the flexor brevis hallucis tendons were inadvertently divided in excising the sesamoids. With one exception, this untoward event occurred only in cases in which both sesamoids were removed. It results in a typical hammer toe deformity, and repair of the tendon or arthrodesis of the interphalangeal joint of the toe is subsequently required to overcome it.



# SUMMARY AND CONCLUSIONS

1. The sesamoid bones of the great toe are essential parts of the human skeleton, appearing early in fetal life, developing in the capsule of the joint by typical intracartilaginous bone formation. Later they become invested by the flexor brevis hallucis tendons. At no time do they appear as part of the phalanx or metatarsal bone.

2. Ossification occurs between the eighth and eleventh years, often from multiple centers which may or may not unite subsequently. Failure of union of these centers is believed to give rise to the partite appearance of these bones seen in the roentgenogram and often mistaken for fracture.

3. Bipartite sesamoid is a frequent anomaly, occurring in at least 10.7 per cent of the feet examined roentgenologically in this clinic. Developmental division occurs in all the sesamoid bones, including the patella. We found the anomaly at the thumb in 6 per cent of the hands examined.

4. Developmental division of the sesamoids does not predispose toward sesamoid pain.

5. Fracture of the sesamoids of the great toe is a rare condition. That diagnosis should not be made unless a previous roentgenogram shows the involved bone to be undivided, or unless subsequent roentgenograms or pathologic sections demonstrate the presence of callus.

6. No specific disease of the sesamoids, such as so-called "sesamoiditis," "sesamoid osteomalacia" and "typical disease of the sesamoid bones," was found in any of the patients operated on at this hospital. The pathologic lesions in our cases, when demonstrable, were arthritis, bursitis and luxation. Other conditions have been assumed, but have not been demonstrated. Several cases in our series showed no demonstrable pathologic condition, and the pain in these cases we believe to be due to localized arthritis not shown in the roentgenogram.

7. Of forty-one patients on whom sesamoidectomy was performed for the relief of pain, we found that 41.5 per cent obtained complete relief, and another 29.3 per cent were definitely improved, making 70.8 per cent who were benefited by the operation. Five patients, or 12.2 per cent, were not improved.

8. Seven patients, or 17 per cent, were relieved of their pain by the operation, but had their flexor brevis hallucis tendons inadvertently cut, thus acquiring a hammer toe deformity for which further surgical measures were indicated. Great care must be exercised in removing the bones from their tendons if this accident is to be averted, especially in double sesamoidectomy.

9. Both sesamoids need not, and should not, be removed unless there is a clear indication for removing each one. To remove both increases the hazard of dividing the tendon, whereas leaving one normal sesamoid in place does not seem to predispose to the recurrence of pain.

10. Incisions should be kept free from weight-bearing surfaces and bony prominences against which the shoe will rub.

11. Sesamoidectomy should be reserved for those cases of painful sesamoids which have failed to respond to conservative methods of treatment.

12. The operation should be supplemented by adequate postoperative physical therapy in the form of massage and early motion at the joint.

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# THE CURLING ULCER

## STUDY OF INTESTINAL ULCERATION ASSOCIATED WITH SUPRARENAL DAMAGE

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PHILADELPHIA

Although Travers,<sup>1</sup> in 1817, first described duodenal ulcer as a definite entity, it was Dupuytren<sup>2</sup> who, in 1826, first called attention to the congestion and inflammation of the mucous membrane of the alimentary tract which may be associated with superficial burns. In 1840, James Long<sup>3</sup> reported the occurrence of duodenal ulcer accompanying severe superficial burns in two young girls, but the credit for first describing the association of these lesions has usually been given to Curling,<sup>4</sup> who in 1842 reported four of his own cases of duodenal ulceration due to burns and eight additional cases which he had collected. This type of duodenal ulcer has, in fact, frequently been called "Curling's ulcer."

### INCIDENCE

Since these original reports, the occurrence of Curling's ulcer has been noted occasionally, but the lesion is apparently by no means frequent. Autopsy records are of doubtful value unless definite evidence exists that the type of lesion which the statistician is interested in was looked for. The data presented here should be accepted only in this light. Perry and Shaw<sup>5</sup> found duodenal ulcers occurring in 0.4 per cent of all cases coming to autopsy and in 3.3 per cent of all patients who died of burns. Fenwick<sup>6</sup> found duodenal ulcerations in 6.2 per

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From the Laboratory of Research Surgery and the Department of Surgery (Division C), University of Pennsylvania.

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cent of all fatalities due to burns. Erichsen<sup>7</sup> found records of two such ulcerations in a series of approximately 13,000 necropsies, many of them in cases of accident and burn. Harris<sup>8</sup> found only a single case of duodenal ulcer in about 500 cases of superficial burns, 138 of which were fatal.

The ulcers are more common in young girls, and are twice as frequent in women as in men. Cases have been reported in children as young as 12 months and in adults up to 70 years of age. They occur most frequently following burns on the trunk. The severity of the burn often is not the determining factor in the production of ulceration, since Maes<sup>9</sup> reported a fatal case following a limited superficial burn. A case of duodenal ulcer following a pelvic burn subsequent to cauterization for cervical carcinoma, after the method of Percy, was reported by Leonard and Dayton.<sup>10</sup>

#### ETIOLOGY

The etiology of the intestinal ulceration following superficial burns is still vague. No explanation so far advanced seems adequate. Curling,<sup>4</sup> in his original article, suggested that the cause of the ulceration lay in a hyperactivity of Brunner's glands, which overact in an attempt to compensate for a skin which cannot function. He believed that the overactivity of the glands leads to hyperemia and subsequent ulceration. Hunter<sup>11</sup> considered the ulcers to be the result of toxins secreted into the duodenum through the bile. The possibility of emboli serving as a cause has been suggested by Billroth<sup>12</sup> and Moynihan,<sup>13</sup> particularly in cases of infected burns. The many additional theories seem so inadequate that they do not warrant further discussion.

#### PATHOLOGY

Curling<sup>4</sup> believed that the ulcers occurred only in the duodenum, but they have since been recognized in all portions of the stomach and the small intestine. The most common site of ulceration, however, is in the duodenum above the ampulla of Vater. Moynihan<sup>13</sup> stated

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12. Billroth, T., quoted by Maes.<sup>9</sup>

13. Moynihan, B. G. A.: *Duodenal Ulcer*, ed. 2, Philadelphia, W. B. Saunders Company, 1912, p. 24.



that 75 per cent of the ulcers are limited to the first portion of the duodenum. The ulcers usually appear in from two to seventeen days after the burn, the average time being from six to twelve days. They are acute, may be long and narrow, and tend to progress rapidly to hemorrhage, perforation or healing, showing little tendency to become chronic. The ulcers may be single or multiple, as many as from forty to fifty being reported in a single case, and they may vary in size from 1 or 2 mg. to several centimeters. Although the mortality has been given as approximately 100 per cent, this is probably correct only in that 100 per cent of the patients whose condition has been diagnosed died, but undoubtedly many who have had ulceration have recovered. A diagnosis of Curling's ulcer is rarely possible during life, death usually resulting from hemorrhage or perforation before the condition is recognized. Moynihan<sup>13</sup> found no cases of perforated Curling's ulcer on record in which treatment was successful.

Premonitory signs suggesting the presence of an acute ulcer are usually lacking, and diagnosis is therefore difficult. In twenty of twenty-nine cases reported by Perry and Shaw<sup>5</sup> perforation or hemorrhage, or both, occurred. Hemorrhage is said to occur more commonly than perforation, the latter usually making its appearance on the tenth or eleventh day after the burn.

The acute ulcer, however, becomes chronic in a limited number of instances. Kirchmayr<sup>14</sup> reported a case of chronic duodenal ulcer developing in a boy in association with a severe burn. The occurrence of spontaneous healing of the intestinal ulceration is certain, such a case having been reported by Curling.<sup>4</sup>

#### RELATION OF SEVERE BURNS TO SUPRARENAL DAMAGE

For some time it has been recognized that superficial burns cause suprarenal damage. Weiskotten,<sup>15</sup> in 1917, in studying a series of six fatal cases of burns, found that hemorrhage and necrosis, which could readily be recognized grossly, had occurred in the suprarenal glands. These conditions and some hyperplasia of the lymphatic glands appeared to him to be the striking pathologic findings in these cases. Similar findings have been reported by Ravdin and Ferguson.<sup>16</sup>

Olbrycht,<sup>17</sup> in 1924, found a reduction of lipoids and chromaffin substance in the hyperemic suprarenal glands following burns. In a series

14. Kirchmayr, L.: Duodenal Ulcer After Burns, *Deutsche Ztschr. f. Chir.* **171**:109, 1922.

15. Weiskotten, H. G.: Fatal Superficial Burns and the Suprarenals, *J. A. M. A.* **69**:776 (Sept. 8) 1917.

16. Ravdin, I. S., and Ferguson, L. K.: The Early Treatment of Superficial Burns, *Ann. Surg.* **3**:439, 1925.

17. Olbrycht, J.: Experimental Research on Deaths from Burns, *J. A. M. A.* **83**:1802 (Nov. 9) 1924.

of five fatal cases of burns in human beings, three in dogs and two in rabbits, he found the suprarenals low in or almost devoid of epinephrine. In 1926, Greenwald and Eliasberg<sup>18</sup> carried out a series of experiments on rabbits. The blood sugar was determined before and after the animals were burned under ether anesthesia. In each case there was a rise in the blood sugar following the burn, the height and rapidity of the rise being dependent on the severity of the burn. The blood sugar never returned to normal before death, although at autopsy the pancreas showed no lesion. In the animals that died early the blood sugar was high, indicating, according to Greenwald and Eliasberg, a marked hyperactivity of the suprarenals and a low glycogen content of the liver. The animals that lived over twenty-four hours showed suprarenal destruction, and there was an associated suprarenal hypofunction leading to a high glycogen content in the liver. The liver and pancreas showed no gross or microscopic change. The authors concluded from this work that during the first few hours after extensive burns, dextrose and epinephrine were contraindicated because of the hyperactivity of the suprarenal glands, but in cases in which the patient survived forty-eight hours, the administration of dextrose and epinephrine would seem important because of the hypoglycemia and the decreased activity of the suprarenal glands.

Lattes<sup>19</sup> carried out chemical analyses of the suprarenal glands in fatally burned animals. He found a reduction of cholesterol to 15 per cent of the normal amount and an associated reduction of the lipids to 65 per cent of the total lipid content of the suprarenal glands. This reduction in the lipids, chiefly cholesterol, coincides with attempts at hyperplasia of the cortical cells, and usually comes in that period, when sudden death may occur. Deaths during this period were thought to be the result of the existing hypoglycemia and exhaustion. Aschoff,<sup>20</sup> who for years has been interested in the pathology of the suprarenal glands, states that suprarenal lipids have a detoxifying function, and that their diminution has a pathologic significance in the causation of death resulting from burns. If the acute stage of the exhaustion is survived, regeneration of the suprarenal cortex usually results.

Epinephrine has been recommended in the treatment of burns for many years by various authors: Plaza,<sup>21</sup> Olbrycht,<sup>17</sup> Nakata<sup>22</sup> and

18. Greenwald, H. M., and Eliasberg, H.: Pathogenesis of Death from Burns, *Am. J. M. Sc.* **171**:682, 1926.

19. Lattes, L.: The Adrenal Glands in Deaths from Burns, *Arch. di farmacol. Sper.* **49**:324, 1930.

20. Aschoff, L., quoted by Lattes.<sup>19</sup>

21. Plaza, A.: Epinephrin in the Treatment of Burns, *J. A. M. A.* **80**:438 (Feb. 10) 1923.

22. Nakata, J.: The Suprarenals in the Severely Burned, *Cor.-Bl. f. schweiz. Aerzt* **48**:1283, 1918.

Ravdin and Ferguson.<sup>16</sup> Recent experimental work seems to establish it as a sound therapeutic measure in certain cases of severe burns in which the patients survive the initial period of twenty-four hours, if the symptoms indicate such therapy.

Since Weiskotten<sup>15</sup> first centered attention on the suprarenals in cases of fatal burn, other authors have reported the presence of suprarenal hemorrhage, often massive, in connection with severe burns. The case reported by Harris<sup>23</sup> is especially interesting. A child  $3\frac{1}{2}$  years of age died with hematemesis on the third day after an extensive first degree burn. Autopsy disclosed a duodenal ulcer with massive hemorrhage about the right suprarenal gland, extending into the perirenal tissues, with many smaller hemorrhages into the left suprarenal gland. The occurrence of suprarenal hemorrhage and necrosis in burns, occasionally associated with intestinal ulceration, suggested to Dr. Ravdin a possible relationship between these lesions.

Elliott,<sup>24</sup> in 1914, reported gastric ulceration following bilateral suprarenalectomy in cats. The gastric juice in these animals examined just before death retained its normal acidity.

Mann,<sup>25</sup> in 1916, performed bilateral suprarenalectomy in sixty dogs, the operation being done in two stages. In forty of these animals ulceration appeared in the stomach or duodenum before they died or were killed. Of forty animals in which only a unilateral suprarenalectomy was done, ulcers appeared in only one dog. The ulceration was of two types: (a) widespread erosions, limited usually to the fundus of the stomach, and (b) punched-out ulcers varying in size from 2 mm. to 2 cm., located usually in the prepyloric region of the stomach. The duodenal mucosa was usually congested, and five dogs showed ulceration in this area. These ulcers usually extended down to the muscularis mucosa, and often a vessel in the base of an ulcer caused hemorrhage. Ligation of the common pancreatic duct or the formation of an external biliary fistula did not prevent the formation of ulcers after bilateral suprarenalectomy. In a group of animals fed soda at four hour intervals, ulceration developed in only one, which suggests acidity as a factor. In a group of ten dogs, posterior gastrojejunostomy was performed between stages of the suprarenalectomy, and in this group ulceration developed in only four. In another series, a loop of jejunum was transplanted behind the stomach, reestablishing the intestinal continuity by an anastomosis below this loop. Suprarenalectomy was then performed

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23. Harris, R. I.: Fatal Burn, Death Due to Hemorrhage into the Suprarenal Capsule and Hemorrhage from a Duodenal Ulcer, *Brit. J. Surg.* **16**:677, 1929.

24. Elliott, T. R.: Some Results of Excision of the Adrenal Glands, *J. Physiol.* **49**:38, 1914.

25. Mann, F. C.: A Study of Gastric Ulcers Following Removal of the Adrenals, *J. Exper. Med.* **23**:203, 1916.

in two stages, and although ulceration appeared in both the stomach and the isolated loop, it was much more pronounced in the stomach. This seemingly indicated that while acidity was a factor, it was not the primary one. Mann<sup>26</sup> found that the ulcers usually appeared at the site of hemorrhage into the mucosa, and he considered that they appeared during the moribund period.

In this connection, the work of Elman and Hartmann<sup>27</sup> is interesting. These authors were able to produce duodenal ulceration in six dogs in which the total pancreatic juice was diverted to the outside through an external fistula. The ulcers were rather large and extended down through the entire mucosa, usually appearing two weeks after the fistula was formed. Berg and Jobling<sup>28</sup> were able to produce duodenal ulceration in thirteen of twenty-three dogs by means of an external biliary fistula, and Kapsinow<sup>29</sup> produced duodenal ulcers in seventeen of forty-three dogs in which all the bile was short-circuited into the terminal ileum through a cholecystenterostomy after ligation of the common bile duct.

Stewart and Rogoff<sup>30</sup> observed gastric and duodenal ulceration in forty-eight of one hundred and eighteen suprarenalectomized dogs and in twenty-nine of a series of eighty-nine suprarenalectomized cats. Blood was occasionally found in the gastro-intestinal tract of these animals at autopsy, and the presence of patches of hyperemia, hemorrhage and atrophy was noted in the pancreas. Levy and Armingat<sup>31</sup> found gastric ulcers in five of six cats in which a two stage suprarenalectomy was performed. The ulcers varied in number from one to sixteen. In none of these animals was any evidence of ulceration found in the small intestine.

Britton<sup>32</sup> and others performed bilateral suprarenalectomy in a series of twenty cats. The average duration of life after operation was 7.5 days.

26. Mann, F. C.: Further Studies on Gastric Ulcers Following Adrenalectomy, *J. Exper. Med.* **24**:329, 1916.

27. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of the Duodenum After Continued Loss of Total Pancreatic Juice, *Arch. Surg.* **23**:1030 (Dec.) 1931.

28. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, *Arch. Surg.* **20**:997 (June) 1930.

29. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, *Ann. Surg.* **83**:614, 1926.

30. Stewart, G. N., and Rogoff, J. M.: Studies on Adrenal Insufficiency, *Am. J. Physiol.* **91**:254, 1929.

31. Levy, M., and Armingat, J.: Suprarenals in the Production of Gastric Ulcers, *Arch. d. mal. de l'app. digestif* **20**:1104, 1930.

32. Britton, S. W.: Observations on Adrenalectomy in Marsupial, Hibernating and Higher Mammalian Types, *Am. J. Physiol.* **99**:9, 1931. Britton, S. W., and Silvette, H.: Some Effects of Cortico-Adrenal Extract and Other Substances on Adrenalectomized Animals, *Am. J. Physiol.* **99**:15, 1931. Britton, S. W.; Flippin, J. C., and Silvette, H.: The Oral Administration of Cortico-Adrenal Extract, *Am. J. Physiol.* **99**:44, 1931.

Bilateral suprarenalectomized dogs survived an average of ten days. After unilateral suprarenalectomy, dogs usually lived for from two to three months, but were found to succumb in a few days if placed on a high protein diet. The blood sugar in the suprarenalectomized animals began to fall with the first indication of suprarenal insufficiency, dropping below 50 mg. per hundred cubic centimeters of blood in over one half of the animals. Consistently there was a rise in the blood urea nitrogen, the values reaching from 40 to 80 mg. per hundred cubic centimeters of blood. Blood chlorides were found to be diminished, while the blood calcium was increased. At autopsy the animals showed congestion of the gastric mucosa, with some ulceration, and an associated congestion of the pancreas. Rats, opossums and ground hogs reacted in a similar manner, both chemically and anatomically. Interestingly enough, ground hogs subjected to bilateral suprarenalectomy during the summer months survived for a period of from one to ten days, while those operated on during the winter lived for from twenty to one hundred and twenty days, usually dying with the approach of spring. Swingle<sup>33</sup> stated that in his work the urea nitrogen was the most valuable index of approaching suprarenal insufficiency.

Best and McHenry,<sup>34</sup> in a recent review of the literature on histamine, called attention to the fact that this substance may be a factor in the production of peptic ulcer. The relationship between histamine and epinephrine was first studied by Dale and Richards,<sup>35</sup> in 1918, and subsequently investigated by Dale,<sup>36</sup> Kelloway and Cowell,<sup>37</sup> Lucas,<sup>38</sup> and others. It has been postulated that many physiologic processes are effected in opposite ways by histamine and epinephrine, and the fact that epinephrine may be liberated from the suprarenal glands with the injection of histamine further suggests that these two substances may be physiologically antagonistic. Dale<sup>36</sup> has shown that bilateral suprarenalectomy appears to increase the sensitivity of the animal to histamine about thirty times. The evidence, however, is conflicting regarding the exact nature of this antagonism, and also whether it is the cortex of the suprarenal, the medulla or both that are active in protecting against histamine.

33. Swingle, W. W., personal communication.

34. Best, C. H., and McHenry, E. W.: Histamine, *Physiol. Rev.* **11**:371, 1931.

35. Dale, H. H., and Richards, A. N.: The Vaso-Dilator Action of Histamine and of Other Substances, *J. Physiol.* **52**:110, 1918.

36. Dale, H. H.: Some Chemical Factors in the Control of Circulation, *Lancet* **1**:1179 (June 8); 1233 (June 15) and 1285 (June 22) 1929.

37. Kelloway, C. H., and Cowell, S. J.: On the Concentration of the Blood and the Effects of Histamine in Adrenal Insufficiency, *J. Physiol.* **57**:82, 1922.

38. Lucas, G. H. W.: Blood and Urine Findings in Desuprarenalized dogs, *Am. J. Physiol.* **77**:114, 1926.

In this connection, McIlroy's<sup>39</sup> report on the production of acute gastric ulceration in cats following the administration of histamine should be noted. Buchner, Liebert and Malloy<sup>40</sup> produced similar ulcers in rats with histamine. O'Shaughnessy<sup>41</sup> was able to produce acute gastric ulcers in cats following the injection of histamine into the layers of muscle in the stomach.

Cushing<sup>42</sup> recently reported three fatal cases of perforated acute peptic ulcer following operations for cerebellar tumor. In a complete review of all the available evidence to date on the neurogenic origin of ulcer, Cushing has collected data which suggest a theory which may lead to an entirely different concept of the etiology of certain peptic ulcers.

I was interested in ascertaining whether or not intestinal ulceration would occur when the suprarenals were only damaged, not removed. Since the Curling type of ulcer undoubtedly occurs in burned patients who survive, I wished to simulate as closely as possible a type of suprarenal damage which would produce no gross evidence of suprarenal insufficiency. Not only did this approach to the subject suggest a possible explanation for the duodenal ulcer seen in cases of severe burn, but it was felt that additional information regarding the etiology of peptic ulcer might be obtained.

#### EXPERIMENTAL DATA

I wish to report observations on twenty-four dogs subjected to varying degrees of suprarenal damage. Of the twenty-four animals, twenty-one were examined at autopsy. Eighteen were subjected to bilateral suprarenal damage, while three had only one suprarenal gland traumatized. The suprarenal cortex was injured chiefly, but the medulla was also traumatized to a lesser extent, a high frequency coagulating current being used. A minimum period of one week to a maximum period of three weeks was allowed to transpire between operations. The animals were killed at varying periods of from one week to one month after completion of the operative procedure.

Congestion involving the mucosa of both the stomach and the small bowel was noted in six cases, being marked in three and moderate in three. Congestion of the mucosa of the small intestine alone was more

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39. McIlroy, P. T.: Experimental Production of Gastric Ulcers, *Proc. Soc. Exper. Biol. & Med.* **25**:268, 1928.

40. Buchner, F.; Liebert, P., and Malloy, P. J.: Concerning the Experimental Production of Acute Peptic Ulcers in the Rat's Stomach, *Beitr. z. path. Anat. u. z. allg. Path.* **81**:391, 1928.

41. O'Shaughnessy, L.: Etiology of Peptic Ulcers, *Lancet* **1**:177, 1931.

42. Cushing, Harvey: Peptic Ulcers and the Inner Brain, *Surg., Gynec. & Obst.* **55**:1, 1932.

striking, being of moderate degree in three animals, marked in seven and extreme in one. Diffuse hemorrhage into the mucosa of the small intestine was noted in one animal, beginning abruptly at the pyloric ring and extending down through the duodenum and upper jejunum (fig. 1). Frank gastro-intestinal hemorrhage with free blood in the stomach and small intestine was present in three dogs.

In seventeen of twenty-one animals definite ulceration was present in the small intestine, being most marked in the duodenum, but also present in the jejunum and upper part of the ileum. In no case was any evidence of gastric ulceration found.

The ulcers were of two distinct types, which I have classified as acute and chronic on the basis of their appearance. In ten animals



Fig. 1 (dog 288).—Extreme congestion of the duodenal mucosa, beginning abruptly at the pyloric ring and associated with free blood in the small bowel. This dog died within twenty-four hours following cauterization of the second suprarenal gland. Numerous areas of superficial ulceration were found in the small bowel at autopsy.

the ulceration was of the acute type (fig. 2), appearing as superficial circular or ovoid areas of mucosal destruction, with clean, punched-out borders extending only partially through the mucosa. From five to ten ulcers were frequently present throughout the duodenum and the jejunum. The average length of life following the first operation in this group of dogs was 17.3 days. Nine of the ten animals had been subjected to bilateral cauterization, while the remaining animal had only one suprarenal gland damaged.

Seven of the seventeen animals presented definite circumscribed ulcers of a more chronic type (fig. 3), with heaped-up edges and excavated craters at autopsy. These ulcers appeared in the duodenum, jejunum and upper part of the ileum, from three to eight being present

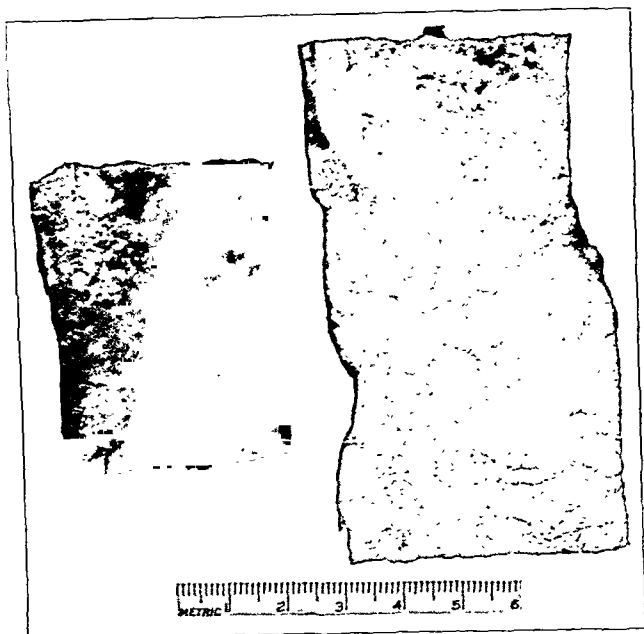


Fig. 2.—Acute superficial ulceration occurring in the duodenum of the dog several days after bilateral suprarenal cauterization. Intense congestion of the mucosa of the proximal duodenum is also illustrated.

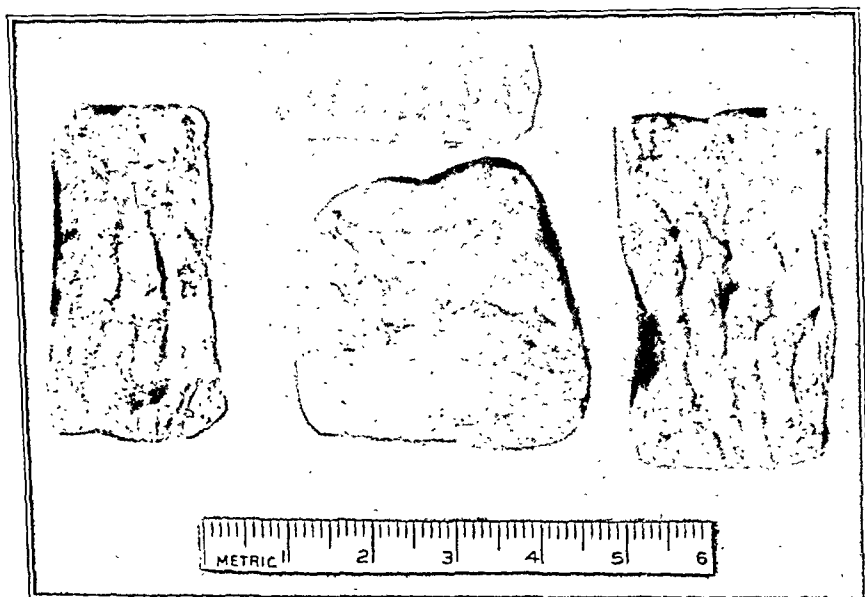


Fig. 3 (dog 433).—Duodenal and jejunal ulceration following bilateral suprarenal cauterization. The dog was killed thirty-two days after the primary operation, and autopsy revealed considerable fresh blood in the gastro-intestinal tract.



in each animal. No ulcers were found above the pyloric ring, although in several animals they began just distal to it. The ulcers extended through the entire mucosa, down to the muscularis mucosa, but there was no evidence of perforation in any case. One animal with fresh blood in its small bowel at autopsy showed an eroded vessel in the base of a small duodenal ulcer, which proved to be the bleeding site. The average length of life in this group of animals following the preliminary operation was 24.5 days. All but two of this group had been

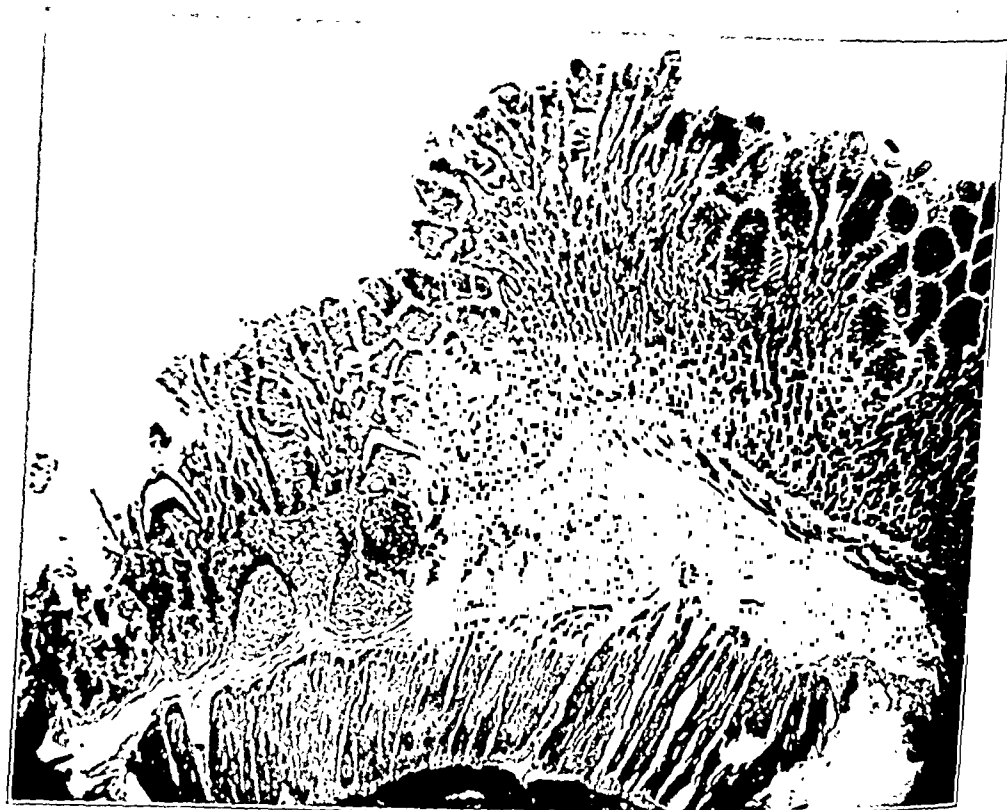


Fig. 4.—Low power photomicrograph through the edge of a "chronic" ulcer, showing the crater overlying an area of lymphoid tissue.

subjected to bilateral suprarenal damage. Ulcers appeared on the bases of Peyer's patches (fig. 4) and in areas where no lymphatic germinal tissue was present. In fact, no definite location on the intestinal wall showed a predilection for them.

Gastric analysis in three animals showed no definite variation from normal. Studies of the blood sugar were made on eleven fasting animals during the postoperative period. The average blood sugar was 82 mg. per hundred cubic centimeters, the lowest being 40 mg. per hundred cubic centimeters and the highest, 126 mg. per hundred cubic centimeters of blood. Tests for sugar tolerance were performed pre-

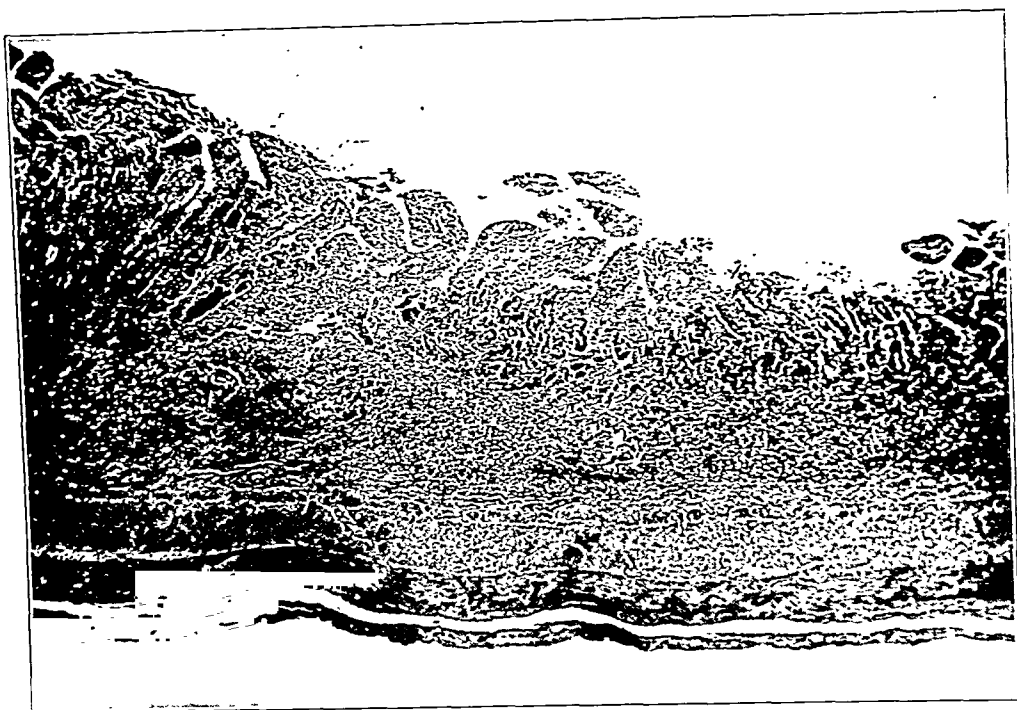


Fig. 5.—Low power photomicrograph of superficial duodenal ulcer following bilateral suprarenal damage in the dog. Destruction of the superficial mucosa is evident.



Fig. 6.—Low power section showing necrosis of mucosal cells. Early stage of formation of deep ulcer following bilateral suprarenal damage. The cellular reaction is apparent. The muscularis mucosa is intact.

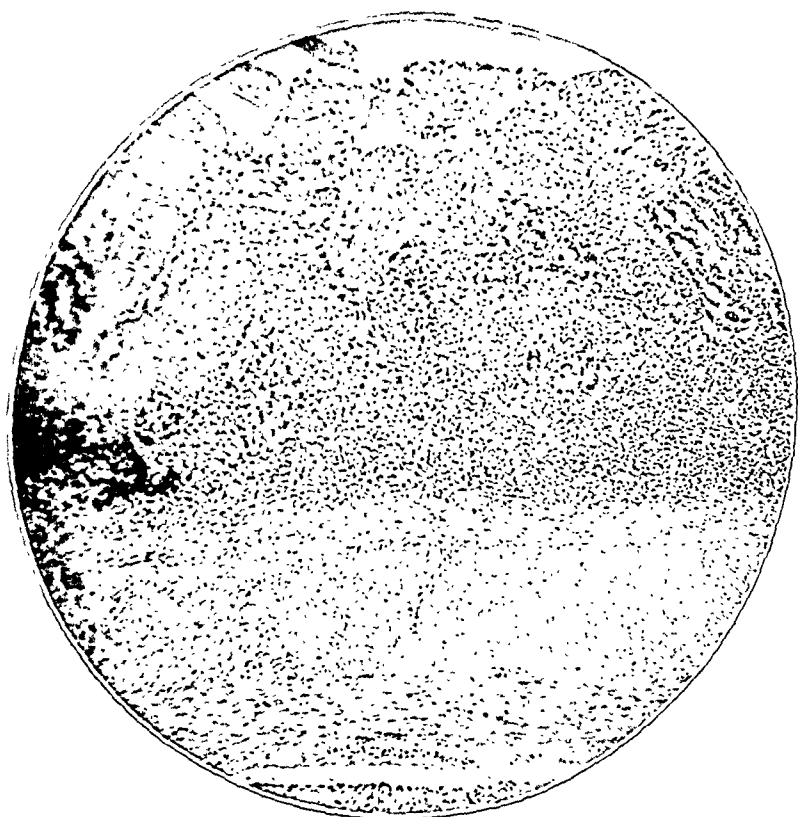


Fig. 7.—High power section through base of the ulcer. Glandular elements have nearly disappeared, and the mucosa is replaced by inflammatory and necrotic mucosal cells.

the postoperative period. These studies suggested that suprarenal insufficiency was not present to any marked degree.

At autopsy the suprarenals showed a varying degree of destruction, with fibrosis and regeneration occurring in some sections. Examination of the pancreas in each instance disclosed no gross lesion.

Microscopic sections of the more superficial ulcers showed a circumscribed destruction of the superficial mucosa, but there was no evidence of any chronic cellular exudate. There were some congestion and hyperemia of the tissues, but the picture was that of an acute ulcerative process without marked cellular reaction (fig. 5).

Sections of the deeper ulcers showed a much more marked destruction of the mucosa; in some places it was almost entirely destroyed (fig. 6). The muscularis mucosa appeared to be partially eroded in some sections, but in none was it completely destroyed. Glandular elements were almost entirely absent from the base of the ulcers, and great numbers of lymphocytes and polymorphonuclear leukocytes were seen in the tissues forming the walls of the craters of the ulcer (fig. 7). No thrombi were visible in any of the adjacent vessels.

#### COMMENT

There can be no doubt that peptic ulcer is being seen more frequently in medical and surgical clinics during recent years. Stimulated by the problems which this increasing number of patients presents, a considerable amount of experimental and clinical data has been published in an effort to explain the origin of the lesions.

In the experimental laboratory, gastric and duodenal ulceration has been produced in animals by many and varied methods. Most of the experimental work has been directed primarily against the stomach or duodenum, on the assumption that peptic ulcer is essentially a local disease. That experimental ulcer can be produced by mechanical, chemical or traumatic procedures cannot be denied. That the fundamental basis for these lesions is always local is open to question.

The concept that peptic ulcer may take its origin on a neurogenic basis is by no means new. Beginning with the work of Rokitansky, to whom credit is given for first suggesting a neurogenic basis for gastro-intestinal ulceration, Cushing<sup>42</sup> recently clearly reviewed the entire subject.

The relationship between the sympathetico-suprarenal system and the parasympathetic nervous system has in recent years been carefully studied. These two systems, in the normal person, presumably exist in a state of balance. A variety of conditions, however, may interfere and alter this relationship, leading to a predominant effect of one system over the other. To quote Cushing:

As far as the stomach is concerned, on this working basis of imbalance between the sympathetic and parasympathetic system, it is known that vagal stimulation causes increased motility and secretion, whereas sympathetic stimulation gives reverse effects; and as a natural corollary vagal paralysis diminishes secretion and motility, whereas sympathetic paralysis increases them, presumably by releasing the vagus from the check normally exercised by the sympathetico-adrenal apparatus against its overactions.

In the balanced relationship existing between the sympathetic and parasympathetic systems, the suprarenal glands play an important part. Bilateral suprarenalectomy has repeatedly resulted in gastric and sometimes duodenal ulceration in various types of laboratory animals. The

effect in such instances is to break an important link in the homeostasis of the animal. In the experiments reported in this paper the link was not completely broken. In fact, as far as I was able to ascertain by chemical studies of the blood, at most only a minor degree of suprarenal insufficiency existed. Nevertheless, seventeen of twenty-one animals on which autopsy was performed showed some type of ulceration of the small bowel.

It is interesting that gastric ulceration was not observed in any instance, although congestion of the gastric mucosa was observed. I am unable to explain why gastric ulcer has been repeatedly observed in the suprarenalectomized animal, while in the experiments reported here, where the suprarenals were only damaged, the ulceration occurred in only the small intestine. It may be thought that this could be explained on the basis that many of the ulcers appeared in the lymphatic follicles, but many had no such background and were situated in such positions on the intestinal wall as to be well removed from any Peyer's patches.

I do not feel justified, with the evidence at hand, in offering any definite explanation concerning the origin of these ulcers. The frequency with which they occur following simple damage to the suprarenal glands, however, suggests that a definite relationship probably exists between the suprarenal glands and the gastro-intestinal tract. Whether the duodenal and jejunal ulceration is the result of a break in the sympathetic chain, with a resultant hyperactivity of the parasympathetic glands acting through the vagus, remains to be definitely proved, although such a sequence of events would seem to suggest itself.

The relationship between suprarenal activity and histamine is as yet also purely conjectural. Dale<sup>36</sup> and Best and McHenry<sup>34</sup> have suggested a physiologic antagonism between these substances, but it is not possible, at this time, to go beyond the mere possibility of such an antagonism existing normally in the organism.

#### SUMMARY

1. Suprarenal hemorrhage, either microscopic or macroscopic, is a common finding in cases of fatal burns.
2. Partial destruction of the suprarenal glands, not sufficiently extensive to cause gross suprarenal insufficiency, results in the rather constant production of ulceration in the duodenum and jejunum of the dog.
3. In a series of twenty-one dogs, seventeen showed definite ulceration in the small bowel after bilateral suprarenal cauterization, but in no case was ulceration seen proximal to the pyloric ring.
4. Perforation never occurred in any of the animals, although gross hemorrhage into the intestinal tract was observed in three instances.

5. In ten animals the ulcers were of the acute superficial type, while in seven ulcerative lesions were revealed at autopsy which both grossly and microscopically appeared more chronic.

6. The possibility that suprarenal damage may disturb the normal balance between the sympathetic and parasympathetic nervous systems is discussed.

7. This experimental work may add further support to the neurogenic theory of formation of peptic ulcer, although the entire subject is not as yet clearly understood.

# POINTS IN THE SURGERY OF THE FRONTAL LOBES OF THE BRAIN

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This paper deals with some of the anatomic and physiologic peculiarities which govern the operative treatment of certain lesions of the contents of the anterior cranial fossae, and includes a description of a method of exposing the latter. It is not intended to be in itself a complete survey of the field; many practical points have been recorded by other surgeons, and reference will be made to these in the appropriate places. Details concerning the various types of lesions are best assembled in papers which are confined to a particular type; because many such studies are now available, it may be not unprofitable to revert now and then to a regional outlook, by attempting to combine in broad outline an account of the surgical difficulties which are the sum, or perhaps even the product, of lesion and site. Although much of what follows may be already familiar to individual surgeons, the paper is based on a considerable experience, which insures that any procedure that is described, and any statement that is made, has at least been subjected to exacting tests.

## POINTS IN THE SURGICAL ANATOMY OF THE COVERING OF THE ANTERIOR FOSSAE

The surgeon is especially interested in the extent of the frontal sinus, in the arrangement of the diploic veins, and in the arrangement of the dura and its vessels. These features are subject to variation with the age of the patient; for example, neither the frontal sinus nor the diploic is fully developed in childhood.

*Frontal Sinus.*—The extent of the frontal sinus may be gaged from roentgenograms of the head. In children it is never extensive enough to be in the line of the lowest perforation of an osteoplastic flap, but in adults it may extend as high as 5 cm. on the forehead. It is traditional to lay stress on avoiding it, but we have never seen harm result from

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From the Section on Neurologic Surgery, the Mayo Clinic.

opening it; such an opening may be plugged with bone wax or covered with animal membrane (Adson) but if the mucous membrane is intact a small bit of muscle is enough. Rarely the sinus may encroach on the base of the bone flap; Logan Turner<sup>1</sup> has recorded a case in which it was limited laterally by the bony wall of the temporal fossa, and mesially extended along the roof of the orbital cavity as far as the anterior edge of the optic foramen.

*Diploic Veins* (fig. 1).—An illuminating paper on the veins of the diploe was published by Jefferson and Stewart<sup>2</sup> in 1928. The subject is naturally of interest to the neurologic surgeon, because it is useful

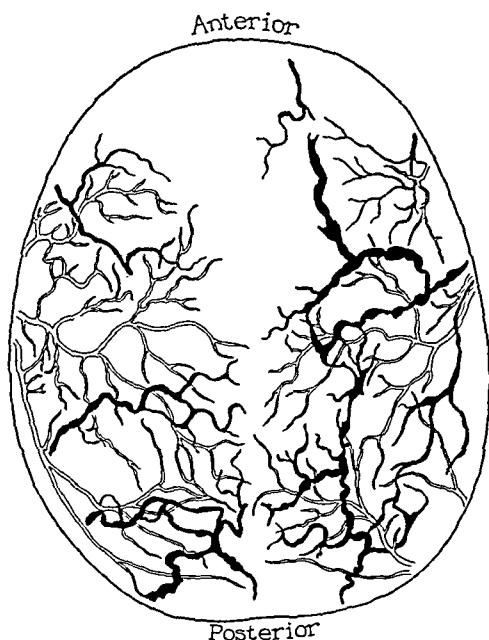


Fig. 1.—The arrangement of the diploic vessels (solid lines) and meningeal vessels (open lines) as viewed from above. (By the permission of the British Journal of Surgery and Messrs. G. Jefferson and Stewart.)

to know the points on the edges of the skull and the bone flap where bleeding from diploic veins is to be expected. The frontal diploic veins take the form of a stumpy "Y," the stalk of which emerges through a small opening in the supra-orbital ridge to join the angular vein. In the temporal part of a bone flap will be the anterior and posterior tem-

1. Turner, A. L.: On the Illumination of the Air Sinuses of the Skull, with Some Observations upon the Surgical Anatomy of the Frontal Sinuses, Edinburgh M. J. 45:460, 1898.

2. Jefferson, Geoffrey, and Stewart, D.: On the Veins of the Diploe, Brit. J. Surg. 16:70 (July) 1928.



poral veins, which converge toward the great wing of the sphenoid, where they communicate with the meningeal veins on the one hand and with the sphenoparietal sinus on the other. It is said that frequently the anterior temporal vein runs more deeply, in the dura, and that its course is represented by the groove anterior to that for the middle meningeal vessels; it ends in the sphenoparietal sinus. It is always necessary to apply bone wax to the cut outer end of the great wing of the sphenoid to check the free oozing which is a result of the anastomosis between diploic veins, meningeal veins and sphenoparietal sinus. Bleeding from the inner surface of the bone flap is venous, and the multitude of small oozing points represents the places of anastomosis between diploic and meningeal veins.



Fig. 2.—Greatly enlarged diploic veins in a case of large right frontal meningioma.

The arterial supply of the bone flap is derived from branches of the deep temporal arteries on the outer side, and from branches of the middle meningeal artery on the inner side. The surgeon makes use of this arrangement when he strips the temporal muscle from below upward from the greater part of the bone flap, to lessen the risk of a postoperative extradural collection of blood. Although this procedure must deprive the bone of most of its remaining blood supply, its vitality is singularly rarely jeopardized.

Not all cases of intracranial tumor are accompanied by dilatation of the diploic veins. In some cases, however, these veins may be so large that the cutting of the bone flap is a formidable business, with the possibility of great loss of blood (fig. 2). In these it is a good plan (as Adson has shown) to cut a broad groove in the bone with ordinary nibbling forceps; it is then possible to plug each canal with wax, which

cannot be done through the cut made by a Gigli saw. This method should also be used for isolating any piece of skull invaded by a meningioma.

*Dura.*—The arrangement of the dura in two layers has been utilized by Elsberg<sup>3</sup> to secure the gradual decompression of tumors in the underlying frontal lobe. The bone of the flap is sacrificed, and the outer layer of the dura stripped off; the increase in intracranial pressure gradually stretches the thin inner layer, which prevents the brain from breaking. This maneuver is well adapted to cases in which intracranial tension is so high that the dura cannot be opened safely, and in such patients, we have used it with satisfaction. The separation is best begun toward the base of the skull, where the line of cleavage is easiest to find.

A man who had a large spongioblastoma multiforme of the left frontal lobe was relieved of his symptoms by this operation in the month of October. We learned of his death in the following March, and that in the interval he had driven a rotary snow plough.

*Middle Meningeal Vessels* (fig. 1).—The middle meningeal artery crosses the great wing of the sphenoid, to divide into anterior and posterior terminal branches. The former runs toward the pterion, and sometimes it is completely surrounded by bone; indeed in one case we saw it appear on the external aspect of the skull, where it was cut when the temporal muscle was incised.<sup>4</sup> It courses toward the vertex behind and parallel to the coronal suture. The posterior branch is directed toward the middle of the parietal bone, over the squamous temporal; here it divides into branches which pass both upward and backward. Jefferson and Stewart have pointed out that the caliber of the middle meningeal artery is larger than is necessary for the supply of the avascular dura alone, and that it is of relatively large size so that it may nourish the overlying bone as well as the membrane.

The branches of the meningeal veins lie between the corresponding arteries and the bone, and they are responsible for the grooves on the inner aspect of the skull. Above they pass to the finely-meshed cavernous systems of the lacunae, the presence of which prevents fierce reflux bleeding from the longitudinal sinus when the veins are divided near the vertex. They communicate freely with the diploic veins; in long-standing hydrocephalus the blood in the diploic veins is likely to collect in pools around these communications.

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3. Elsberg, C. A.: The Rôle of the Dura Mater in Cranial Decompressive Operations; Note on the Preservation of the Inner Layer of the Dura in Cranial Decompression Operations, and on the Use of the Outer Dural Layer for the Plastic Closure of Dural Defects, *Ann. Surg.* 87:15 (Jan.) 1928.

4. This anomalous course was the cause of a musical murmur synchronous with cardiac systole, and loudest over the gap in the bone.

## POINTS IN THE SURGICAL ANATOMY OF THE FRONTAL LOBES

*Form.*—The form of a frontal lobe, as encountered on the operating table, differs from that of an anatomic specimen. As Macewen<sup>5</sup> emphasized, the mesial portion of the orbital surface is not flat, but dips downward to fill up the not inconsiderable trough floored by the cribriform plate of the ethmoid bone; during elevation of the lobe, this difference in levels in the floor of the anterior cranial fossa must be borne in mind.

*Arteries* (fig. 3).—The arterial supply of the frontal lobe is derived from two sources, the anterior and the middle cerebral arteries. When the surface of the lobe is exposed by craniotomy, it is useful to remember that its edges are nourished by the anterior cerebral artery, and its

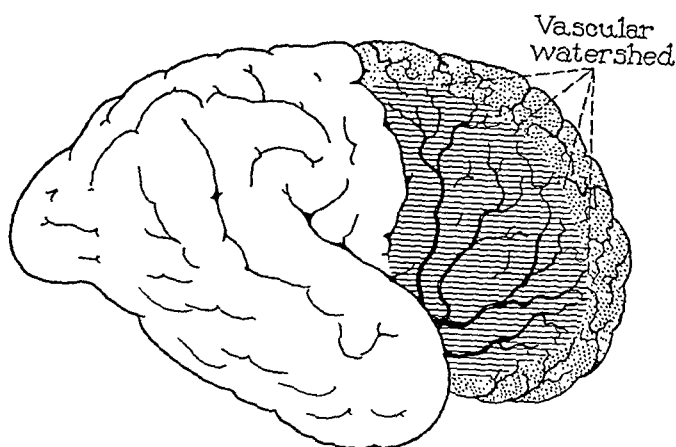


Fig. 3.—The arteries of the outer aspect of the right frontal lobe, showing the vascular watershed.

central part by the middle cerebral artery. The branches of the former appear over the rim of the lobe, and pass over its surface to supply the upper and lower frontal convolutions and the anterior part of the middle frontal convolution. The branches of the latter radiate from the sylvian point to supply the remainder of the lobe. This arrangement has a bearing on the directions in which incisions into the lobe are to be made. Although it is true, as Cobb<sup>6</sup> has pointed out, that the superficial arteries of the brain are not "end-arteries," because they are connected by a wide capillary bed, nevertheless the occlusion of any one of them leads to disturbances of nutrition in its area of supply. Obviously, therefore,

5. Macewen, William: *Atlas of Head Sections*, Glasgow, James Maclehoese and Sons, 1893.

6. Cobb, Stanley: *The Cerebral Circulation: XIII. The Question of "End-Arteries" of the Brain and the Mechanism of Infarction*, *Arch. Neurol. & Psychiat.* 25:273 (Feb.) 1931.

when it is possible, incisions into any part of the cerebral cortex should be made parallel to the vessels, and in the watershed between the two sources of arterial blood, the brain should be uncapped (to use the term introduced by Cushing<sup>7</sup>) until the edges of the opening are well within the territories of both arteries.

Under certain conditions it is desirable to remove (uncap) the anterior end of a frontal lobe, in order to improve the access to baso-frontal or hypophyseal growths. Naturally because of the intellectual functions of the frontal lobes this maneuver is employed as seldom as possible; but we have not noted any prohibitive degree of intellectual impairment after its use. The watershed between the territories of

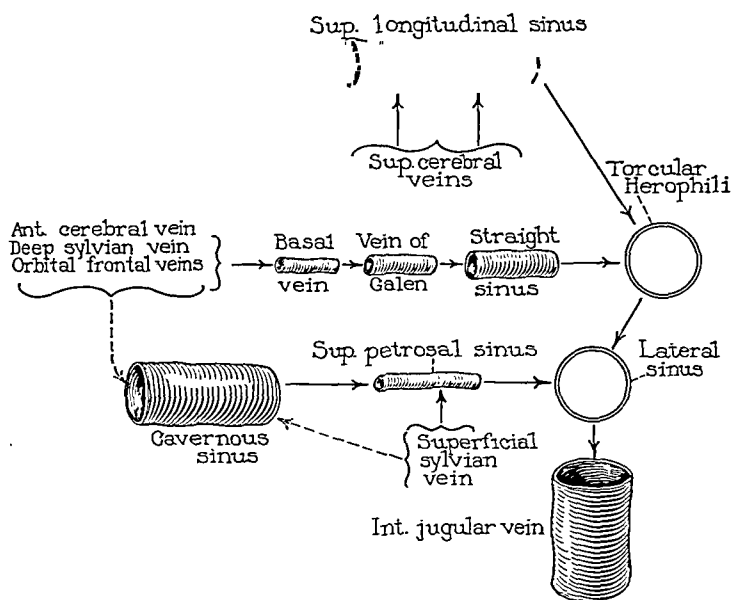


Fig. 4.—The venous drainage of a frontal lobe.

the anterior and middle cerebral arteries forms a convenient line to mark the limits of amputation. When lobectomy is judged to be the best method of treating an intracerebral growth, the amputation may be carried 3.5 cm. posteriorly from the frontal pole before the cavity of the ventricle is reached.

*Veins* (fig. 4).—The veins of the frontal lobe that are exposed by frontal craniotomy are arranged in superior and inferior groups.<sup>8</sup>

7. Cushing, Harvey: *Intracranial Tumors*, Springfield, Ill., Charles C. Thomas, 1932.

8. Browning, William: *The Veins of the Brain and Its Envelopes: Their Anatomy and Bearing on the Intracranial Circulation*, New York, F. B. O'Connor, 1884. Sargent, Percy: *Some Points in the Anatomy of the Intracranial Blood Sinuses*, *J. Anat. & Physiol.* **45**:69 (Jan.) 1911.

The superior group consists of two named veins, the frontal and the precentral, and perhaps two or three smaller unnamed veins. The veins of this group begin in small venules about a finger's breadth above the level of the horizontal limb of the fissure of Sylvius. Occasionally an additional vein passes upward between the named veins; this is the superior branch of the superficial sylvian or Trolard's vein, and it connects the latter with one of the superior cerebral veins, or with the longitudinal sinus; sometimes it is so large that it seems to be the chief superficial vein for the anterior part of the hemisphere. These veins increase in size as they approach the longitudinal sinus; from about half an inch to an inch from their termination they leave the surface of the

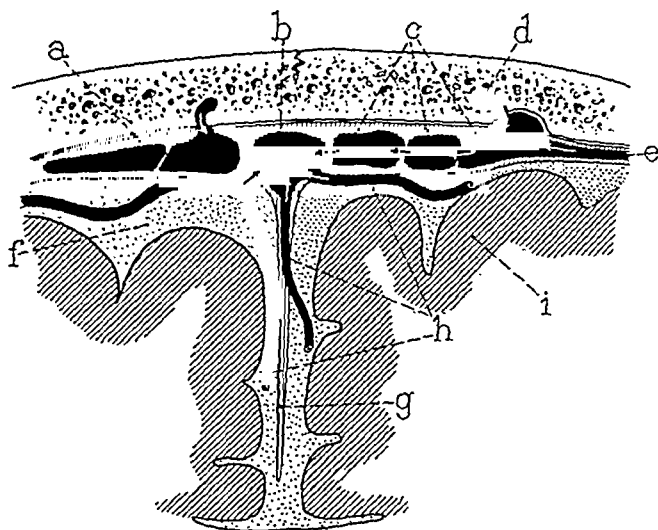


Fig. 5.—The ways in which the cerebral, meningeal and diploic veins reach the longitudinal sinus; *a*, dura mater; *b*, longitudinal sinus; *c*, lacuna; *d*, diploic veins; *e*, meningeal vein; *f*, subarachnoid space; *g*, falx cerebri; *h*, cerebral veins, and *i*, cerebral cortex.

brain, cross the subarachnoid space, and apply themselves to the deep surface of the dura mater, usually where it forms a lacuna. Commonly there will be two lacunae in the field of operation, a small frontal lacuna under which the frontal vein disappears, and the anterior end of the large parietal lacuna, under which the precentral vein disappears. It has been pointed out by Stopford<sup>9</sup> and by Le Gros Clark<sup>10</sup> that almost always the cerebral veins do not open into the lacunae, but into the sinus directly (fig. 5). The close application of the cerebral veins to the under surface of the lacunae is therefore deceptive; the lacunar afferents

9. Stopford, J. S. B.: The Functional Significance of the Arrangement of Cerebral and Cerebellar Veins, *J. Anat.* 64:257 (April) 1930.

10. Le Gros Clark, W. E.: On the Pacchionian Bodies, *J. Anat.* 55:40 (Oct.) 1920.

belong to the meningeal and diploic venous systems. This anatomic arrangement is not without surgical significance; it allows an operator to stop the bleeding from a lacuna without interfering with the return of blood from the hemisphere. Commonly the terminal part of each venous trunk is joined by a vein from the mesial surface of the lobe; not infrequently, however, the latter veins enter the substance of the falx cerebri about midway between its upper and lower borders, and pass upward to the longitudinal sinus. When they are at all enlarged they may offer a formidable obstacle to the displacement of the lobe from the falx.

The frontal vein approaches the sinus at a right angle, and the pre-central vein is inclined somewhat forward. The openings of the cerebral veins into the sinus are "so constructed and arranged that they are permanently open,"<sup>9</sup> and it has been suggested that this provides a physiologic mechanism to maintain a pressure in the cerebral veins sufficient to withstand the pressure of the cerebrospinal fluid. The distortion of these veins by parasagittal tumors has been dealt with by Elsberg<sup>11</sup> in a valuable paper.

The inferior group comprises the veins which drain the lower and under aspects of the lobe, and they join the cavernous and superior petrosal sinuses. Two named veins follow the sylvian fissure, a superficial (vein of Trolard<sup>12</sup>) and a deep vein. The former follows the fissure; at its anterior end the vein penetrates the dura at the outer end of the small wing of the sphenoid, curves around over the floor of the middle fossa and ends either in the superior petrosal sinus or in the cavernous sinus; this vein is to be safeguarded if the frontal lobe must be displaced. The deep vein lies at the bottom of the sylvian fissure, and when it reaches the anterior perforated space, it unites with the anterior cerebral vein from the longitudinal fissure, and with veins from the orbital surface of the lobe, to form the basal vein of Rosenthal.<sup>13</sup> The basal vein curves backward around the crus cerebri to join the vein of Galen.

No hard and fast rule can be laid down regarding the neurologic complications which may follow ligation of these vessels. At least in the child, the longitudinal sinus is said to communicate at its anterior end with the veins of the nose, so that after its occlusion there is a possible channel for the return of the blood. However, ligation or

11. Elsberg, C. A.: The Parasagittal Meningeal Fibroblastomas, *Bull. Neurol. Inst.*, New York 1:389 (Nov.) 1931.

12. The term "vein of Trolard" is not infrequently, but incorrectly, applied to the vein that connects the superficial sylvian vein with one of the superior cerebral veins or with the longitudinal sinus.

13. Occasionally these tributaries of the basal vein open into the cavernous sinus.

resection of the sinus is seldom necessary, even for the removal of parasagittal meningiomas. The nearer to the rolandic fissure a ligature has to be placed, the more likely is paresis to appear; fortunately this is usually temporary. Tears in the sinus are best sealed with pledgets of muscle; if necessary, these may be held firmly against the tear by anchoring sutures, passing from the dura of one hemisphere to that of the other.

Ligation of the cortical veins themselves is rarely unavoidable; occasionally, however, their upper ends may course over a tumor from which they cannot be separated. The degree and extent of the paralysis which follows their purposeful occlusion varies with the pattern of the veins. We have seen a case in which ligation of the upper end of the precentral vein was not followed by any gross paralysis; in another case, ligation of the lower end of the precentral vein was followed by hemiplegia, which improved somewhat in the course of time. In a third case, in which the superior branch of the vein of Trolard was tied during the removal of the parasagittal meningioma, a permanent brachial monoplegia resulted.

#### SURGICAL DIAGNOSIS OF TUMORS OF FRONTAL LOBES

In certain circumstances the final localization of a tumor of the frontal lobe may require preliminary surgical measures. These circumstances may be grouped as follows: (1) when it is certain that an intracranial tumor is present, but no localizing feature can be found; (2) when, as not infrequently happens, the clinical picture is in keeping either with a tumor of one frontal lobe, or with a tumor of the opposite cerebellar lobe, and (3) when it is tolerably certain that a tumor is growing in one of the frontal lobes, but there is doubt as to the side. Ventriculograms will decide any of these difficulties, but it may be possible to dispense with the injection of air and to rely for the diagnosis on the results of ventricular puncture.

Tumors of the frontal lobes do not always affect the ventricular system in the same way. Those that are near the foramina of Monro may obstruct the flow of fluid from one or both lateral ventricles, so that these become dilated; the dilatation is often unequal, and is then greater on the side opposite to the tumor. When the growth is situated in the anterior part of a frontal lobe, dilatation of the ventricles is absent, and the ventricle on the side of the tumor may contain much less fluid than normally.

A tumor of a frontal lobe gives rise to a characteristic filling defect in the anterior horn of the corresponding lateral ventricle (fig. 6). If the tumor is large and is situated on the mesial aspect of the lobe, a similar filling defect may be apparent in the opposite anterior horn also.

This pressure must be transmitted through the falx cerebri, and the occasional occurrence of these contralateral filling defects shows that the falx is by no means a rigid partition. Naturally, bilateral filling defects are found in the presence of a bilateral parasagittal tumor such as a meningioma, or of a tumor of the corpus callosum.

For the surgical localization of tumor of a frontal lobe it is best, and often quickest, to tap both lateral ventricles. If a small ventricle, containing only a few cubic centimeters of fluid, is encountered on one side, the procedure need not be prolonged, for this finding not only rules out cerebellar tumor, but also lateralizes the growth. When both



Fig. 6.—Characteristic filling defect in the anterior horn of the lateral ventricle produced by a tumor in the frontal lobe.

ventricles are found to be dilated, it is wisest to proceed with the injection of air, because only in this way can a diagnosis be made between supratentorial and infratentorial growths. Although the dilatation may be marked enough to raise a suspicion that the growth is below the tentorium, if it is in a frontal lobe its presence will be betrayed by a filling defect shown in the lateral ventriculogram. When the filling defect is bilateral, the growth may be lateralized by inspection of the anteroposterior ventriculogram; the ventricular system is always displaced away from the side on which the growth (or, in the case of a bilateral tumor, most of the growth) is present. When the fluid obtained by ventricular puncture is xanthochromic, it is likely that the tumor impinges on or invades the ventricular system.



## OPERATIVE TECHNIC

*Methods of Approach* (fig. 7).—Various methods are in use for exposing the contents of an anterior fossa, or anterior fossae. When a unilateral exposure is desired, the bony part of the flap is placed so as to give the required access, and the choice of skin incision varies with the preference of the surgeon. Thus it may conform to the outline of the bone flap (Cushing, Adson); it may be shaped to turn forward as a broad-based flap, whereas the bone flap turns outward (Naffziger,<sup>14</sup> Frazier<sup>15</sup>), or it may be made parallel to the coronal suture (Souttar,<sup>16</sup> Learmonth<sup>17</sup>). Excellent access is also given by an osteoplastic flap, the base of which, both skin and bone, follows the supra-orbital ridge and a corresponding

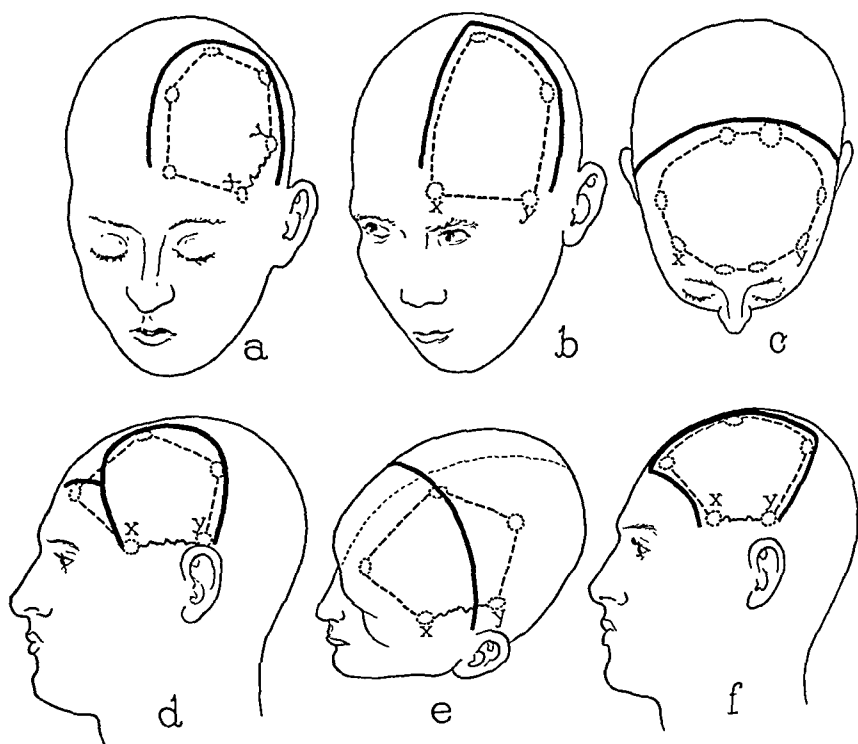


Fig. 7.—Various osteoplastic flaps used to expose the frontal lobes: *a*, Naffziger's and Frazier's flap; *b*, Sachs' unilateral flap; *c*, Sachs' bilateral flap; *d*, Adson's flap; *e*, Souttar's and Learmonth's flap, and *f*, Cushing's flap; *x-y* indicates the base of the bony part of the flap.

level in the temporal fossa (Sachs<sup>18</sup>). When both anterior fossae must be exposed, the procedure may be the forming of bilateral osteoplastic flaps, opening outward,

14. Naffziger, H. C.: Personal communication to the authors.

15. Frazier, C. H.: Differential Diagnosis of Lesions in and Adjacent to the Sella Turcica, *Am. J. Surg.* **16**:199 (May) 1932.

16. Souttar, H. S.: Hunterian Lecture on New Methods of Surgical Access to the Brain, *Brit. M. J.* **1**:295 (Feb. 25) 1928.

17. Learmonth, J. R., and Kernohan, J. W.: Three Cases of Epidermoid Cyst of the Brain, *S. Clin. North America* **11**:853 (Aug.) 1931.

18. Sachs, Ernest: *The Diagnosis and Treatment of Brain Tumors*, St. Louis, C. V. Mosby Company, 1931.

and cut either through a coronal incision or through incisions in the skin corresponding to the outlines of the bone flaps; or, as Sachs prefers, the roof of both fossae may be turned forward on a base which follows the supra-orbital ridges. Before the bone is lifted off the superior longitudinal sinus, Sachs recommends that the sinus be freed from the bone; when making a bilateral exposure we prefer to leave a girder of bone, however slim, over the sinus, because the bone flaps can be firmly secured to it at the end of the operation.

*Technic.*—For some time we have used the technic, a description of which follows, to obtain access to the contents of the anterior cranial fossa. It is described in detail, not as an improvement on other methods but as a procedure which has been satisfactory in every way.

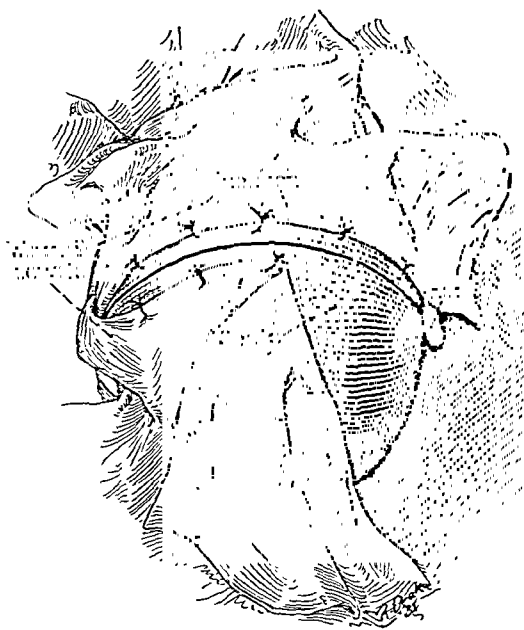


Fig. 8.—Method of attaching drapings.

We have used local anesthesia whenever possible, supplemented by the administration of a suitable dose of one of the barbiturates the night before operation, and again an hour or so before the injection is made. If the patient wishes a general anesthetic, for reasons which will be stated this is best continued through an intratracheal tube. The patient is placed on the operating table with the face pointing upward, and the occiput resting in a "doughnut" made of cotton wool.

The incision (fig. 7 *c*) passes across the head, in the line of the coronal suture; the advantages of an incision of this type have been enumerated by Souttar. The scar is within the hair line, and this may have an economic as well as a cosmetic appeal. It divides the scalp in the watershed between the territories of the internal and external carotid arteries. When the osteoplastic flap is replaced, the line of the incision in the scalp is not superimposed on the incisions in the cranial bones. It is often unnecessary to make the long tragus-to-tragus incision described by Souttar; this is indispensable only when it is possible that a bilateral exposure may have to be secured. When the operation is to be strictly unilateral, for example in dealing with a hypophyseal adenoma, the incision may be stopped halfway between

the median line and the tragus of the opposite side; an additional incision perpendicular to this, and passing anteriorly to the hair line, may be added, or the incision may be slanted, so that it begins at the tragus and ends at the hair-line of the opposite side, midway between the median line and the zygoma. The chosen incision is marked lightly on the skin, and then four towels are sewn in place along it (fig. 8); at the ends, an effort should be made to embrace the temporal vessels in the grasp of one of the sutures, and when the anterior towel is being fastened a suture should be placed in the line of each supra-orbital artery, in an endeavor to control these vessels. If these hemostatic sutures are successfully placed, bleeding from the incision is minimal. As the incision is made, bleeding from its posterior edge is controlled in the usual way by the application of hemostats to the galea, for they aid retraction by their weight; on the anterior edge we have found it most convenient to use the skin clips employed by Adson, which are as effectual and not so cumbersome (fig. 9). When the incision has been completed, wound towels are sewn to the galea aponeurotica (fig. 10).

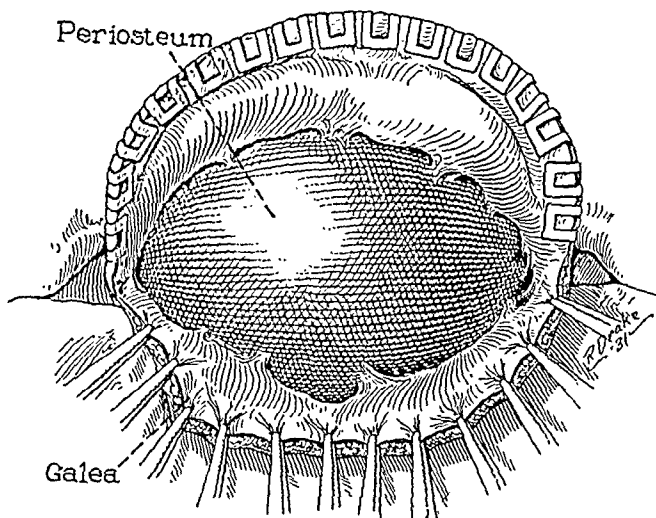


Fig. 9.—Method of controlling bleeding from the edges of the incision.

The scalp is then stripped from the forehead and everted, until the supra-orbital margin is reached, where the supra-orbital artery may have to be tied; if a general anesthetic is being used, the "scalping" is least hindered by the use of an intra-tracheal tube. The scalp is also stripped backward about 5 cm. to the posterior limits of the proposed incision in the bone. The edges of the incision are kept apart by some form of self-retaining tractor. We have found it advisable, for cosmetic reasons, to make the perforation near the nasion with a trephine; before this is done, a flap of periosteum with its base over the supra-orbital ridge is turned forward from the site chosen for the perforation (fig. 10). In men, because of the possibility of baldness, the mesial middle perforation may also be made with a trephine. The total number of perforations required will vary; when the skull is thick, and when the vascular channels on the inner table have prominent banks, closer spacing of the perforations makes for ease in passing the guide for the Gigli saw.

After the bone flap has been broken outward, the intracranial pressure may be so great that it would be unwise to open the dura. If a tumor is present, and it is cystic, the intracranial pressure can be sufficiently reduced by partial evacuation of

the cyst through a brain cannula, or a spinal puncture needle of large bore; the cyst can be more easily identified later, if it is not completely emptied. If the tumor is solid, the intravenous injection of 100 cc. of a 50 per cent solution of dextrose will often lower the intracranial pressure enough to allow the surgeon to open the dura. When the dura has been opened, access to the hypophyseal region and to the orbital surface of the frontal lobe is improved by allowing the head to fall backward, when the weight of the frontal lobe will tend to displace it from the orbital plate of the frontal bone (fig. 11).

The methods of dealing with meningiomas exposed by craniotomy of this type have been discussed in a practical manner by Elsberg. If a subcortical tumor is suspected, it may be sought for, and when found, delimited by cautious punctures with a brain cannula; for this purpose we have found it best to employ the stilet of

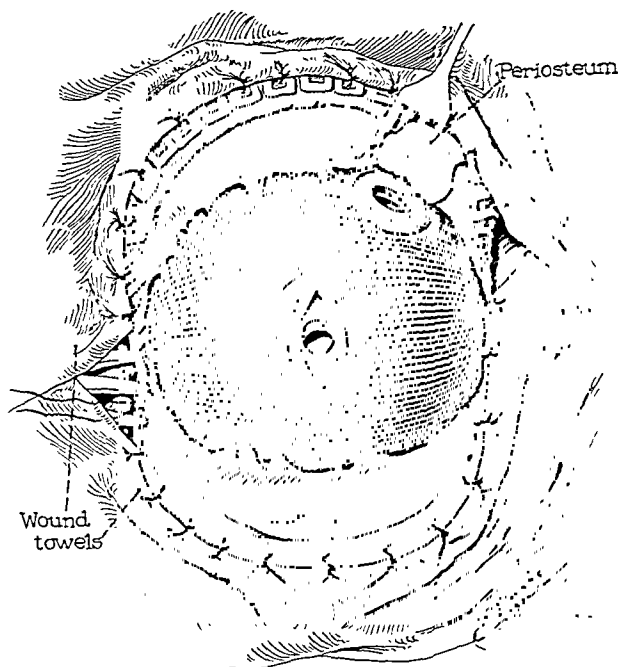


Fig. 10.—Wound towels have been sewn to the galea. Anteriorly a flap of periosteum has been retracted, and the disk of bone beneath it has been removed by a trephine.

a stout hypodermic needle, to which an olive tip has been fused, the resilience of the shaft of this "seeker" making it very sensitive to changes in the consistence of the brain tissue.<sup>19</sup> If a tumor of the glioma group is found, the surgeon must decide either to be content with providing decompression, or to attempt the removal of the whole or part of the growth. Although this is a general problem, its various aspects may be considered in this section.

Whatever the peculiar circumstances of the case, certain generalizations are available to aid in the decision. The surgeon is concerned lest, as a result of his operation, the patient remain aphasic or his intellect be blunted. The former condition arises when the growth involves the so-called speech center on either side. On

19. This suggestion was made by Dr. H. E. Robertson of the Mayo Clinic.

the whole, it has been our experience that whether the defect in speech is the result of pressure on, or actual invasion of, Broca's area, the risk of producing permanent and complete aphasia is rarely so great as to prohibit a radical attack on a relatively benign growth. Moreover the presence of so-called motor aphasia does not necessarily reduce the intellectual capacity of the patient. With regard to the latter condition, we may begin by stating that our own experience coincides with that of Sachs that lesions of a particular frontal lobe, for example the left in right-handed persons, do not lead to a more profound intellectual defect.

The most striking change in personality that we have met was in a right-handed woman, who had an astrocytoma in the right frontal lobe. She had a mild disposition before her illness, and the only feature in her case, other than bilateral choked disks, was the periodic occurrence of violent outbursts of anger, in one of which, she attacked her son-in-law with a pitchfork.

The problem of conservation of intellect is therefore present regardless of the site of the tumor. The largest issue may be taken first; it has been the collective

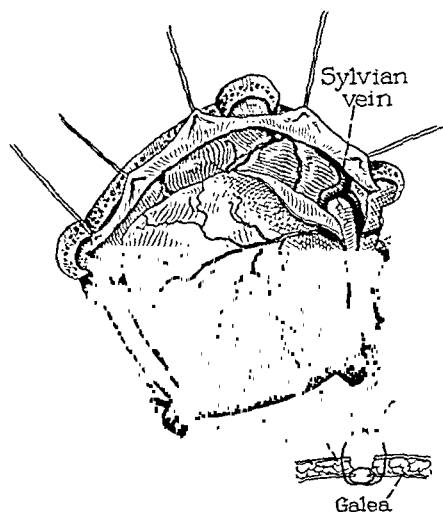


Fig. 11.—A dural flap has been fashioned. The superficial sylvian vein may be noted leaving the hemisphere to pass into the dura of the middle fossa. The inset shows a figure-of-eight suture for closing the skin and galea.

experience at the Mayo Clinic, that primary frontal lobectomy for tumor has been almost invariably followed by some degree of permanent mental impairment, which sometimes has been so extreme as to be socially and economically objectionable. Therefore we hardly ever employ this type of operation. The problem of local partial or total removal of a growth is best viewed from the standpoint of pathologic anatomy. Tumors confined to the pole of the lobe can be removed without much risk of intellectual impairment, and for this there are developmental and architectonic reasons. When the tumor occupies the body of the lobe, the decision is more difficult. When the tumor is cystic, or when it is partially or wholly encapsulated, it is likely that the fibers about it have been displaced and compressed, and thus physiologically blocked; in these circumstances, a radical attempt at extirpation is likely to be followed by restoration of function rather than by further impairment, and all neurosurgeons are familiar with the rapid and often dramatic improvement in mentality which may occur during an operation of this nature. On the other hand, ill defined tumors such as astrocytomas grow

between the fibers, often without compromising their function, and any attempt at extirpation must perforce include with the tumor tissue physiologically intact cerebral pathways. Large tumors of this histologic nature are probably best treated by decompression only, for their life history is so prolonged that the interests of the patient are best served by relief of the increase in intracranial pressure; as Holmes<sup>20</sup> has emphasized, many "mental" symptoms are due wholly to generalized increase in intracranial pressure. Paradoxically enough, in the case of the most malignant spongioblastoma multiforme, its pseudo-encapsulation suits it for subtotal removal, as providing the greatest relief during the short period which its host has still to live.

Other factors may influence the surgeon's decision. The wishes of the patient's friends must be consulted, and if possible those of the patient himself. It may be that grave risk must be taken in an effort to afford the patient an interval of mental clarity during which he can settle financial or domestic affairs; an excellent example of the successful shouldering of this responsibility is quoted by Cushing. The economic condition of the patient and his family is a ponderable factor, for, on the one hand, more radical measures may be employed when one is sure that if physical and mental symptoms persist, adequate care is available during the remainder of the patient's life, without imposing an intolerable financial and personal problem on his friends; on the other hand, occasional aberrations which would be

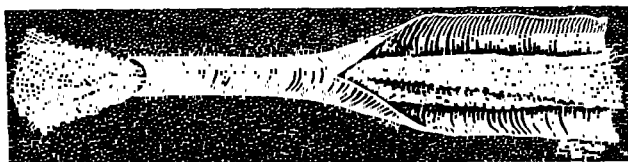


Fig. 12.—Drain for craniotomy wounds.

merely fantastic in an unskilled laborer might lead to irretrievable catastrophe in a person occupying a position of financial or professional responsibility.<sup>21</sup>

One other pathologic point may be mentioned: when the "tumor" proves to be composed of blood vessels, our experience coincides with that of Bailey and Cushing, that it is best not to attack it directly. It has been the practice at the Mayo Clinic to treat these lesions by decompression, followed by adequate roentgenotherapy, and the results have been as satisfactory as the operation has been safe.

When the intracranial part of the operation has been completed, we are in the habit of covering with Cargile membrane any part of the cortex uncovered by dura; the piece of membrane is shaped to lie under the edges of the incision in the dura, and is kept in place by replacing the dural flaps over it. However, when there is any possibility that a cyst may have to be retapped, we do not place membrane over the area of cortex that will be traversed by the needle, because the tough membrane may interfere with the puncture.

In cases in which cerebral tissue has been removed, and in those in which the intracranial pressure following operation is likely to be low, we invariably leave a drain in position. The drain consists of a soft rubber tube, slit at one end, and

20. Holmes, Gordon: Discussion on the Mental Symptoms Associated with Cerebral Tumors, *Proc. Roy. Soc. Med. (Sect. Neurol. and Sect. Psychiat.)* 24: 997, 1931.

21. Bailey (personal communication to the authors) also emphasizes this point.

containing a wick of gauze (fig. 12). It is laid along the base of the flap, with its cut end flattened over the brain as a guard, and the end of the gauze resting on the outer end of the small wing of the sphenoid bone. It is brought to the surface through a small stab wound over the posterior inferior end of the incision in the bone, about 3 cm. behind the main incision. A waiting suture is left in the stab wound. Surgical drainage of craniotomy wounds is a bogey which should be stripped of its terrors; we have never seen any infection as a result of it, or any prolonged leak of cerebrospinal fluid, and we have never had to deal with post-operative hematoma in a case in which a drain had been used.

After the bone flap has been shaped, if desired, for decompression, it is replaced and sutured to the skull by three threads of strong silk, passed through drill holes corresponding to its anterior and posterior ends, and its upper angle. Fixation of the bone flap holds it in position until the wound in the bone has consolidated, and thus in the case of an inoperable growth helps to avoid the formation of a large cerebral hernia, a complication which is as distressing and repugnant to patient and to surgeon as any in the practice of surgery. The disk of bone from the forehead is replaced, and its periosteum sutured over it.

At this stage, if hypertonic solutions have been used, and the brain is still lax (as after operations on the hypophysis), it is a good plan to give 1 or 2 liters of physiologic salt solution intravenously; this restores the bulk of the brain and obliterates the space between the frontal pole and the dura.

Finally the incision in the skin is closed. In the absence of any high degree of increase in intracranial pressure, this is conveniently and quickly carried out by figure-of-eight sutures, which embrace the galea aponeurotica in the small loop of the 8. When the intracranial pressure is high, galea and skin are sutured separately. At each end of the wound a small rubber dam drain is inserted toward the nasion. These allow the scalp to fall against the skull, and they may be removed in forty-eight hours, when their exit is closed by a waiting suture. Finally the head is firmly bandaged with a gauze bandage, the "drift" of which is made to run from forehead to occiput, so that the scalp is pressed into position.

*Postoperative Treatment.*—Any oozing which occurs after the wound is closed is or should be venous; the patient is therefore returned to a bed, the head of which is elevated, to diminish the likelihood of the formation of a postoperative clot. If there has been a reduction in the bulk of the brain, as a result either of shrinking and retraction (as after operations for hypophyseal growths), or of removal of tissue (as after extirpation of tumors), the patient should lie face forward for about twelve hours; this position encourages the frontal lobe to flow forward against its bony case, and thus minimizes the risk of intradural or extradural bleeding. If the intracranial pressure remains high, as after palliative decompression for bulky growths, we have thought that there seemed to be less trouble from cerebral edema as a result of dislocation of the tumor, if the patient lay with his head pillowed on the side of the operation, so that gentle pressure was maintained on the flap. In such cases an effort may be made to anticipate and prevent the edema, by the intravenous administration of hypertonic solutions two or three times a day. The amount of these injections, and their content of dextrose, will vary with the amount of fluid which the patient is able to take by mouth. In spite of every precaution it sometimes happens, as has been emphasized by Cushing, that the redistribution of the intracranial contents which follows decompression leads to the development of cerebral edema. This complication most often follows the decompression of a spongioblastoma multiforme. Its onset may be fulminating; if local anesthesia is being used, the patient may become comatose on the operating table, and if he has been under the influence of a general anesthetic he may not

recover consciousness when it is discontinued. Both these events are of exceedingly grave omen, and although the patient may live several days, we cannot recall an instance of either in which the patient responded to treatment, and ultimately survived. When this complication seemed imminent, in cases in which the opposite lateral ventricle was dilated, we have tried the effect of draining it for a day or two with a flanged cannula or a ureteral catheter, but without any consistent amount of success.

After successful interventions, patients who have been mentally clouded often regain their intellectual faculties rapidly. In other cases, the process of mental restoration is gradual, and in still others it may occur rapidly, after an interval during which operation seems at first sight to have been disappointingly valueless. During such transitional stages, careful nursing is of great importance; the burden of nursing care may be greatly lightened by the use of a retention catheter, and the regular cleansing of the bowel by enema. The nurse's greatest difficulty is often the overcoming of an unreasoning negativism on the part of the patient, and this may make his feeding a crucial problem. In such cases, the quickest solution of the difficulty is to feed through an indwelling nasal tube, on a concentrated fluid diet rich in vitamins. If the season is suitable, the sooner the patient can be taken out of doors the better, and these airings not infrequently prove to be the turning point in his convalescence.

In an uncomplicated case the drain in the suture line and that in the flap are shortened in twenty-four hours, and removed in forty-eight hours. When a drain has not been used, lumbar puncture performed on the first and second days helps to rid the cerebrospinal fluid of any broken-down red blood corpuscles. If the frontal subarachnoid pathways for the absorption of cerebrospinal fluid have been interfered with as a result of a destructive operation on a frontal lobe, it may be several days before the necessary readjustments are made in the disposal of the fluid, and after removal of the drain it may be necessary to assist the absorbing system by aspirating, with a needle and syringe, collections of blood-stained cerebrospinal fluid under the flap.

Now and then a patient who seems to be making a satisfactory recovery dies with a suddenness that does not give time for treatment; in these rare cases death appears to be due to respiratory failure, and the features of the accident suggest pulmonary embolism, but at necropsy no macroscopic reason for fatality can be found.

If figure-of-eight stitches have been used to close the skin, they are cut on the seventh day, allowed to loosen overnight, and removed on the eighth day. When the skin and the galea aponeurotica have been closed separately, the sutures in the skin may be removed in two days. In either case, at the end of ten days a simple ointment applied as a dressing for a day or two will remove any crusting from the scar.

#### OPERABILITY OF TUMORS OF THE FRONTAL LOBES

During the eighteen years from 1914 to 1931, one hundred and eighty tumors involving one or both frontal lobes have been verified histologically at the Mayo Clinic, either at operation or at necropsy. Of these, one hundred and sixty-two were observed during the period of ten years from Jan. 1, 1922, to Jan. 1, 1931. The pathologic diagnosis of these growths is shown in the tabulation.

These figures cannot be utilized to determine the incidence of each type of tumor, because many cases have been excluded in which a



glioma was probably present, but was not verified. On the other hand, from the point of view of the practicing neurosurgeon they can be used to determine the number of each type of growth which he may expect to encounter at operation.

If the table is examined in this way, the first striking figure is the unusually high percentage of meningiomas found in the frontal region. In our series they amount to 41.7 per cent of all verified growths, in contrast to 13.4 per cent, the proportion of meningiomas occurring in Cushing's series of 2,023 verified tumors of the brain as a whole. This high frequency of meningiomas is explained by the occurrence in the frontal region of two basal sites of election for such growths, the meninges covering the olfactory grooves and the meninges in the neighborhood of the sella turcica. Thus of our seventy-five meningiomas,

*One Hundred and Eighty Cases of Tumor of, or Involving, the Frontal Lobes*

Histologic Diagnosis	Cases	Per Cent
.. .. .	75	41.7
.. .. .	4	2.2
Hemangioblastoma.....	5	2.8
Gangliocytoma.....	2	1.1
.. .. .	1	0.6
.. .. .	42	23.3
Spongioblastoma polare.....	8	4.4
Astrocytoma.....	17	9.4
.. .. .	5	2.8
.. .. .	6	3.3
Oligodendroblastoma.....	9	5.0
Ependymoma.....	3	1.7
Sarcoma.....	1	0.6
Lymphosarcoma (metastatic).....	1	0.6
Adenocarcinoma (metastatic).....	1	0.6
	180	100.1

thirty-three were situated on the convexity of the lobe, twenty-one were parasagittal, five were suprasellar and sixteen were attached to an olfactory groove.

Meningiomas of the convexity of the frontal lobes, including parasagittal meningiomas, are nearly always operable,<sup>22</sup> although the difficulties and dangers attending their removal vary widely from operation to operation. The most easily dealt with are the rounded growths presenting solely on the outer surface of the lobe and wholly intradural. Involvement of the skull and of the scalp at once increases the technical difficulty of extirpation, although the problem of dealing with the defect in the bone has recently been simplified by the suggestion of Nafziger, that the tumorous bone be boiled and replaced as an autogenous graft; our colleague Craig has used this device in two recent cases, with most

22. We say "nearly" always, because we have seen a case in which a tumor had been present for more than thirty years. It had resisted several attacks, and had finally come to involve almost the whole of one side of the skull, as well as erupting into the temporal muscle.

happy results. A more difficult problem is the removal of parasagittal growths; their small presenting area, close to the median line, belies the often huge bulk of tumor hidden between hemisphere and falx. Moreover their attachment corresponds to the area of confluence of the cerebral and meningeal veins with the longitudinal sinus. Precise directions for the management of these veins have been given by Elsberg. Here it may be added that when it seems advisable to increase exposure by incising the brain, advantage may be taken of the vascular watershed, to which reference has been made; thus the growth may be uncapped by removal of the edge of the lobe supplied by the anterior cerebral artery. Although such a procedure violates the rule that incisions into the brain should be made parallel to its arteries, it has the compensating advantage of being placed parallel to the long association tracts. Most difficult of all to deal with are parasagittal meningiomas which are bilateral. There is no royal road to their successful removal; only slow deliberate manipulations are possible, and the difference between success and failure often depends on the judgment of the operator as to how much his patient can tolerate at one sitting.

The intricacy of the important structures around the growth makes the removal of a suprasellar meningioma a difficult surgical problem; Cushing and Eisenhardt<sup>23</sup> have recorded the relations of a number of specimens. The process of disentangling the growth from such adjacent structures as the optic nerves and chiasm, the anterior cerebral arteries and the wall of the third ventricle may tax the endurance of both patient and surgeon. It has been suggested by Cushing that greater freedom of manipulation could be obtained by deliberate division of the optic chiasm, and the anterior communicating artery occasionally binds down the growth in much the same way as the chiasm. The division of this artery between clips would not, in the majority of instances, lead to any arterial insufficiency, but it must be remembered that in a certain number of cases the anterior cerebral artery of one side is the direct continuation of the anterior communicating artery, and in such a case division of the latter vessel would be at least hazardous. A meningioma in this situation sometimes follows the arteries in its growth, so as to form a tumorous sleeve for them, and such tumors are obviously inoperable; we have met with one specimen, in which the only vessel in the circle of Willis not enclosed in a layer of tumor tissue was the left posterior communicating artery.

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23. Cushing, Harvey, and Eisenhardt, Louise: Meningiomas Arising from the Tuberculum Sellae, with the Syndrome of Primary Optic Atrophy and Bitemporal Field Defects Combined with a Normal Sella Turcica in a Middle-Aged Person, *Arch. Ophth.* 1:1 (Jan.): 168 (Feb.) 1929.

Meningiomas of the olfactory grooves are generally operable. Occasionally, as in a neglected case which we saw, the tumor may ultimately invade the lateral mass of the ethmoid bone, and in such a case prudence would dictate that at least the lower part of the growth be left undisturbed. In securing adequate exposure of large growths in this region, the principle of uncapping the frontal lobe through the arterial watershed may be usefully employed.

We have alluded to the treatment of angioblastic growths. The solitary epidermoid cyst encountered in our series was easily evacuated.

With regard to gliomatous tumors, of a total of ninety specimens, forty-two, or almost half, were identified as spongioblastoma multiforme; their complete enucleation is an impossible achievement, although, as has been mentioned, partial removal is usually in the best interests of the doomed patient. Of the seventeen astrocytomas, six tumors were cystic and contained a removable mural nodule. Some consideration has been given to the factors which guide the surgeon in dealing with solid specimens, and they apply to all the more slowly growing gliomas. In brief, we believe that the smaller the tumor, and the more anteriorly it is situated, the more radical should be the attempt at extirpation. Larger and more ill defined tumors, that approach the rolandic fissure, we prefer to deal with by decompression alone. A further pathologic point may be emphasized: On more than one occasion we have extirpated such growths because the immediate histologic diagnosis has been astrocytoma, only to be disappointed by the later finding that sections cut at leisure from various parts of the tumor showed areas which conformed to the histologic picture of spongioblastoma multiforme. There appears to be a not inconsiderable group of such growths, and this fact has deterred us from, rather than encouraged us in, attempts at the more radical treatment of large infiltrating gliomatous tumors.

# A REVIEW OF MODERN TREATMENT OF BURNS

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## HISTORICAL DATA

Grecian mythology teaches that of all the animals man was the last race created, and in consequence thereof was most poorly endowed with physical gifts. So Prometheus stole fire from the hearthstone of the gods on Mount Olympus and bestowed it as a gift which would set man apart from all other animals. And so it has. But the sword with which civilization was founded is a two-edged one, and since time immemorial the followers of Aesculapius have sought to bring relief to those luckless mortals who have felt its bite.

The remedies that have been employed in the treatment of burns are legion. But after all, the treatment of burns has developed along certain paths to reach its present state. At the beginning of 1800 physicians were not so far away from the lard and aromatic oils of Hippocrates, and the first great improvement was the antiseptic treatment. Pirrie, of Aberdeen, in 1867<sup>1</sup> advocated the use of phenol after hearing Lister read a paper on its antiseptic value. Morris,<sup>2</sup> in 1882, in this country, was the next strong advocate of antisepsis in the primary dressing. The principle of strict surgical cleanliness did not receive the endorsement it deserved until the beginning of the present century, as almost every burn was promptly smeared with some grease and then the patient was taken to a physician for treatment, thus making primary antisepsis a practical impossibility. The next advance was in learning that the burned patient had to be treated just as energetically as the local lesion itself, and Parker,<sup>3</sup> in 1844, was one of the first to urge treatment of the patient for shock. This principle was not stressed until late in 1880, and the significance of the observations of Cumin<sup>4</sup> in 1823 and of Baraduc<sup>5</sup> in 1862 relative to the increased

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1. Pirrie, W.: On the Use of Carbolic Acid in Burns, *Lancet* 2:575, 1867.

2. Morris, R. T.: The Local Treatment of Burns, *M. Rec.* 22:653, 1882.

3. Parker, W.: Burns and Scalds, in Cooper, Samuel: *A Dictionary of Practical Surgery*, ed. 7. New York. Samuel S. and William Wood, 1844, p. 140.

4. Cumin: *Edinburgh M. & S. J.* 19:337, 1823.

5. Baraduc: *Unione med.*, May 19, 1863.

viscosity of the blood in extensive burns did not receive its just due until the present century. Now the local lesion and the patient are treated with equal vigor.

Enthusiasm for treatment of the local lesion was somewhat lukewarm until Passavant<sup>6</sup> introduced the continuous submersion method to replace the time honored occlusive dressings of oils and ointments. The continuous bath has its advocates today, particularly for infants, but it is not universally practicable, and hence is not widely used. In 1887, Copeland<sup>7</sup> made a radical departure from the older methods and introduced the open air treatment, by enclosing the burned area in pasteboard boxes and allowing nothing but air to touch the local lesion. This treatment had no followers of note until 1905, when Sneve<sup>8</sup> again brought it forward. From 1905 to 1914 there were many controversies between the two schools of practice, and when Barthe de Sandfort<sup>9</sup> introduced paraffin wax, or "ambrine" as it was originally known, many clinicians adopted this new type of closed dressing. However, its disadvantages were many, and the search for a better local treatment was carried on through extensive clinical laboratory research. The culmination was reached in 1925, when Davidson<sup>10</sup> produced his classic work on the use of tannic acid.

#### PATHOLOGIC CHANGES IN BURNS

Burns are classified according to their depth. The older classification of Dupuytren included six degrees, but clinicians of today, particularly in England, Germany and this country, recognize only three: burns of first degree, or simple erythema; those of second degree, or blistering, and those of third degree, or charring.

A burn is a coagulation necrosis of the structure involved and gives rise to the same inflammatory phenomena as occur in any other wound. Lee's<sup>11</sup> table shows the similarities between the pathologic phenomena of burns and those of inflammation.

Burns	Inflammation
1. Erythema, or first degree, equivalent to	Hyperemia
2. Blistering, or second degree, equivalent to	Exudation
3. Charring, phlegmon, or third degree, equivalent to	Necrosis
4. Suppuration	Suppuration
5. Cicatrization	Repair

6. Passavant: *Deutsche Klin.* **10**:348, 365 and 373, 1858.

7. Copeland, W. P.: *The Treatment of Burns*, *M. Rec.* **31**:518, 1887.

8. Sneve, H.: *The Treatment of Burns and Skin Grafting*, *J. A. M. A.* **45**:1 (July 1) 1905.

9. Barthe de Sandfort, E.: *Bull. Acad. de méd., Paris* **71**:560 (April 14) 1914.

10. Davidson, E. C.: *Tannic Acid in the Treatment of Burns*, *Surg., Gynec. & Obst.* **41**:202, 1925.

11. Stewart, F. T., and Lee, W. E.: *A Manual of Surgery for Students and Graduates*, ed. 6, Philadelphia, P. Blakiston's Son & Co., p. 169.

A burn, therefore, should be regarded as a surgical wound. Although it exhibits all the phenomena commonly associated with a surgical wound, it presents one striking difference in that a wound is a solution in the continuity of a given structure, whereas a burn of the skin, for example, is a solution of the vital continuity of that structure, but not of its physical or mechanical continuity. This I believe to be the outstanding characteristic of the burn wound, and failure to recognize this distinction has made the successful treatment of burns a controversial subject for centuries, the despair of predecessors and above all, "a consummation devoutly to be wished." No other type of injury can cause solution of the vital continuity with preservation of the physical or mechanical continuity of so large an area of tissue as a burn.

#### PATHOLOGIC PHYSIOLOGY OF BURNS

The normal, healthy, unbroken skin is composed of a cellular or epidermal layer, the corium or connective tissue layer, in which are embedded some of the hair follicles and sweat glands, and the main vascular or capillary bed. The delicate capillary walls form a closed system. Each individual cell of the tissues constitutes a unit unto itself, receiving its food and oxygen and giving up its waste products through a membrane by means of osmosis and diffusion. In a burn these structures are subjected to great heat, which may destroy the epidermal cell layer and leave the corium, through which pass the majority of the sweat glands and hair follicles, to end in the subcutaneous fat. This is strikingly shown in second degree burns of Negroes, in whom the burned area resembles a white polkadot dress with thousands of tiny black spots, each representing hair follicles and sweat glands (fig. 1). The physical continuity of the corium is unaltered, but its vital continuity is greatly changed. The outer layer of cells is destroyed; the deeper cells are so injured that cellular unity is lost, and the intracellular contents pour out. The capillary walls are broken down, and each tiny vessel stands wide open ready to receive into its lumen any substance with which it comes in contact. The blood plasma, containing many enzymes and ferments of which little is known, pours out through the open capillaries and mingles with the liberated intracellular contents containing proteases and other digestants essential to cell activity, forming a fluid medium in which chemical changes begin at once. The skin is composed largely of protein material which is broken down by the heat, and this is subjected to the action of the various chemicals now present. The whole area becomes a seething layer of biochemical activity, truly a stewpot of the "Grim Reaper," the brew from which must needs be absorbed directly into the blood stream of the unfortunate victim of a burn. Each systole of the patient's heart adds

fuel to the flame by pumping fresh plasma into the mixture, and each diastole sucks away from it the highly toxic products newly formed.

Clinical experience and experimental research have shown the toxic products poured so rapidly into the blood stream to be fraught with dire possibilities. Many different substances have been found, but no one specific toxin has been isolated. The majority of investigators agree that the chief offender is some product of protein metabolism which is manufactured at the site of the burn;<sup>10</sup> its manufacture and absorption begin at the inception of the burn, and enough to produce death may be absorbed within the first twelve hours (Vogt<sup>12</sup>).

The absorption of toxic products occurs mainly within the first twenty-four hours, by which time the reparative processes close the open capillaries, and any absorption thereafter is by osmosis through



Fig. 1.—Tanned membrane peeling off. Second degree burn in a Negro boy.

the reestablished walls of the capillary bed. Robertson and Boyd<sup>13</sup> have shown that a lethal amount can easily be absorbed within the first eight hours; hence the primary treatment is of utmost importance in preventing subsequent toxic shock.

Normal skin is a most efficient insulator and heat regulator of the body. The destruction of large areas of skin results in a marked loss of body heat through radiation (Lee<sup>11</sup>), with an increase in shock pending the application of proper treatment. The advantage of keeping the burned patient in a very warm room or near a fire was recognized at an early date, but the reason for it only recently became generally known and accepted, largely through studies made during the

12. Vogt, E.: Versuche ueber die Uebertragbarkeit des Verbrennungsgiftes. *Ztschr. f. exper. Path. u. Therap.* 11:191, 1912.

13. Robertson, B., and Boyd, G.: *Toxemia of Severe Superficial Burns*, J. Lab. & Clin. Med. 9:1, 1923.

World War. The benefit derived from the widely used electric light cradle is due to the constant maintenance about the patient of a higher temperature than the normal body temperature, which prevents loss of heat from the patient's body.

The fluid lost at the site of a burn is the whole plasma of the blood (Underhill<sup>14</sup>). Until the capillary walls have been repaired there is a steady depletion of the blood plasma which finally results in, first, a marked concentration of the blood, as shown in a number of cases cited by Underhill and his co-workers,<sup>15</sup> and secondly, in extreme dehydration due to the mobilization of all available water in the tissues. It is the increased viscosity of the blood which soon offers so great a resistance to contractions of the heart muscle that shock is either produced or increased.

The total plasma proteins and the total plasma volume drop during the first twenty-four hours, but if the patient recovers they return to normal within the next few days. When the toxemia increases during this latter period, the loss of plasma proteins continues even though the volume of plasma remains normal; in such cases the loss of proteins occurs throughout the capillary bed of the entire body, owing to the alteration of its permeability produced by the absorbed toxin (Davidson and Matthew<sup>16</sup>). Coincident with the loss of plasma at the site of the lesion is a marked loss of sodium chloride. This can be estimated by a determination of the blood chloride, and an effort can be made to replace it. In this connection it has been shown that an animal can lose and compensate for the loss of from 3 to 36 per cent of its total sodium chloride content of the blood (Underhill, Kapsinow and Fisk<sup>17</sup>).

#### MECHANISM OF DEATH FROM BURNS

From a clinical standpoint, mortality from burns is divided into three major divisions: (1) deaths within the first twenty-four hours from primary shock; (2) deaths in from one to three weeks following injury accompanied by all the evidences of a marked toxemia, or those from secondary toxic shock, and (3) deaths from sepsis. This gen-

14. Underhill, F. P.: Changes in Blood Concentration with Special Reference to the Treatment of Extensive Superficial Burns, *Ann. Surg.* **86**:840, 1927.

15. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. T.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment, *Arch. Int. Med.* **32**:31 (July) 1923.

16. Davidson, E. C., and Matthew, C. W.: Plasma Proteins in Cutaneous Burns, *Arch. Surg.* **15**:265 (Aug.) 1927.

17. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: V. Relationship of Blood Chlorides to the Chlorides of Edema Fluid Produced by Superficial Burns, *Am. J. Physiol.* **95**:334, 1930.



erally accepted classification is not accurate as my associates and I have had two deaths from primary shock that continued beyond twenty-four hours, but it is sufficiently practicable to be followed in the present study.

This review covers two hundred and five cases of burns seen during the past thirteen years, from 1920 to 1932, inclusive. There were forty deaths, a mortality of 19.5 per cent. Twenty-seven deaths (67.5 per cent) were from primary shock, and thirteen (32.5 per cent) from secondary toxic shock.

All the deaths in the first twenty-four hour period occurred during profound shock. Not all of the patients were in a state of severe shock on admission, but the development of this profound shock was rapid, coming on from three to eight hours after the burn without preliminary delirium. This emphasizes the great importance of immediate and energetic treatment. Patients surviving the primary shock but dying from secondary toxic shock later can be divided into two distinct clinical groups. The first group (and the larger in this series) after thirty-six hours shows evidences of a marked toxemia by increase in temperature and pulse rate, both of which remain high as the patient becomes restless, irrational and finally frankly delirious, and dies from four to eight days following the burn. Nine of our cases were of this type, presenting the clinical picture of a progressive toxemia with fatal issue.

In the second group the temperature is usually above 100 F., and the pulse rate ranges from 90 to 110 during the first ten days. The appearance, from the standpoint of ultimate results, is most deceptive. After ten days or so, and for no apparent reason, diarrhea, anuria, or both, or some other untoward symptom develops; the patients become irrational and delirious, go into a state of profound shock and die with dramatic suddenness. We had four deaths of this character.

Primary shock is the main cause of death from burns. Reduction of the mortality rate calls for immediate, strenuous treatment to overcome it. The basic etiology of shock from any cause is not understood, but the outstanding clinical characteristic of shock is a failing circulation. Circulatory failure, vasomotor impairment or paralysis occurs primarily from either or both of two general causes. The heart muscle fails to function adequately when subjected to a powerful biochemical depressant, such as a drug or a bacterial or other toxin, or when the mechanical load is too great for the normal cardiac reserve. The influence of a burn toxin on the cardiac mechanism in this early period cannot be ignored, but the extreme circulatory weakness may be explained largely on a more mechanical basis when one recalls that the amount of work done by the heart is tremendous, being estimated at 102,332 foot-pounds of work every twenty-four hours.

Underhill, Kapsinow and Fisk<sup>18</sup> have shown that the volume of blood plasma poured out at the site of a burn is enormous. In animals burned over one sixth of the body surface, the amount lost was 70 per cent of the total volume of blood. They estimated in clinical cases in which one third of the body surface of a 160 pound man is burned that 7,000 cc., or approximately 140 per cent of the total volume of blood, may be lost at the site of injury. They reasoned that this may represent the limit to which the organism can give up its reserve water without losing its normal volume of blood, and when the limit of tissue water mobilization is exceeded a fatal outcome is considerably augmented by the inability of the organism to furnish water to maintain blood of a consistency compatible with adequate circulation.

Further experiments with colloidal and noncolloidal dyes by the same workers<sup>19</sup> indicate that the loss of plasma occurs almost entirely during the first twenty-four to thirty-six hours, and mainly during the earlier hours of this period. In severe burns the concentration of the blood is marked and rapid. It is much easier to prevent concentration of blood than to restore the normal level after a high concentration is established. The explanation for this is based on purely physical laws. The water equilibrium between the blood stream and the tissues is the resultant of two osmotic forces. The colloids of the tissue tend to pull water from the blood stream into the tissues, while the colloids of the blood stream pull water from the tissues. When the whole plasma of the blood escapes in a burned area, the osmotic pressure of the remaining cellular contents is greatly increased as the amount of colloid per unit volume is greater. The available tissue water is then drawn into the circulatory system to reestablish blood volume at the expense of dehydration of the tissues. If the fluid drawn from the tissues remained in the blood stream, probably no ill effects would ensue, but it is promptly poured out, while the cellular elements of the blood remain and again increase the concentration of blood. When the tissues have no more water to give up, the mechanical resistance offered by the increased viscosity of the blood so increases the work of the heart that it falters, and profound primary shock begins to develop. Any fluid now introduced into the circulation cannot be retained because the depleted power of the blood colloids is overwhelmed by the tissue colloids, which continue to draw water into the dehydrated tissues until their force is reduced by dilution.

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18. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: III. The Extent of Edema Fluid Formation Induced by Superficial Burns, *Am. J. Physiol.* **95**:325, 1930.

19. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Studies on the Mechanism of Water Exchange in the Animal Organism: II. Changes in Capillary Permeability Induced by Superficial Burns, *Am. J. Physiol.* **95**:315, 1930.

To summarize, during the first twenty-four to thirty-six hours the burned area acts as an open valve through which pour out first the blood plasma, then the mobilized tissue water and finally the water introduced from without minus the toll taken from it by the dehydrated tissues. After the first twenty-four to thirty-six hours, the capillary openings close, and the water equilibrium is reestablished provided an abundance of fluids is supplied during this period.

#### DEATHS FROM SECONDARY TOXIC SHOCK

For the past twelve or fourteen years medical opinion has leaned toward the theory of secondary toxic shock, and this tendency has been strengthened by recent experimental work and pathologic studies. Weiskotten,<sup>20</sup> in 1919, in ten fatal cases of burns found widespread pathologic changes rather uniformly distributed. The suprarenals were swollen and deeply red, with considerable edema of the perisuprarenal fat. Microscopically, the lesions were comparable to the central necrosis of chloroform poisoning. The most marked changes were found in the patients who had lived the longest. In the lymphatic tissues the lesions progressed for about three days, and then apparently regressed. His conclusion was that "these pathological conditions can be explained only by the presence of a poison, circulating in the blood stream, and having more or less specific action on certain cells of the body." Olbrycht,<sup>21</sup> after postmortem studies, concluded that in severe burns the most extensive changes are in the suprarenals; the amount of damage is roughly proportional to the extent of the burn and the patient's age, being most pronounced in the young. The suprarenals in his cases showed the same changes as occur in anaphylactic shock and peptone intoxication, and he ascribes them to toxins resulting from decomposition of protein material in the burned tissue. The necropsy observations in fatal cases are similar to those in deaths from a specific poison circulating in the blood stream, as in diphtheria.

Vogt,<sup>12</sup> after establishing parabiosis between two animals, burned one of them, and both showed evidence of toxemia. His observation was confirmed by Vaccarezza.<sup>22</sup> Vogt<sup>12</sup> further showed that under conditions of parabiosis (1) the burned animal did not develop as severe a toxemia as when it was alone; (2) the unburned animal did not develop any toxic symptoms when it was separated from the burned one within the first twelve hours, and (3) when the animals were left united, they both died of toxemia. Robertson and Boyd<sup>13</sup> burned

20. Weiskotten, H. G.: *Histopathology of Superficial Burns*, J. A. M. A. **72**:259 (Jan. 25) 1919.

21. Olbrycht, J.: *Experimental Research on Death from Burns*, *Rev. de méd* **41**:81, 1924; *abstr.*, J. A. M. A. **83**:1802 (Nov. 29) 1924.

22. Vaccarezza, R. A.: *Sur la cause de la mort par les brulures*, *Compt. rend* Soc. de biol. **86**:1114, 1922.

rabbits with hot metal plates, and toxic symptoms developed after from twenty-four to thirty-six hours. Burns of the skin, fat or muscle produced toxemia. Removal of the burned tissue by excision less than eight hours after the burn saved the animals from all toxemia. The burned area, removed several hours after the infliction of the burn, was grafted onto healthy animals, and toxemia developed in all such recipients within an hour. Extracts from pieces of burned skin from 1 to 2 cm. square would produce death or severe symptoms when injected into a 200 to 300 Gm. guinea-pig. Extracts made from normal skin or from the skin of animals burned after death produced no ill effects. Injection of the blood serum from a burned animal resulted only in anaphylactic reaction. Injection of whole blood from the burned animal caused marked toxemia in every instance, even though small amounts were used. Davidson<sup>10</sup> reported the cases of two patients in whom the decomposed protein material was precipitated by tannic acid and later covered with hot boric compresses. These patients promptly showed symptoms of severe toxemia, and one died. He expressed the belief that "when the colloids holding toxic substances were rehydrated, the toxic substances were again made available for absorption."

Opposing the theory of toxemia, recent experimental work by Underhill and his associates<sup>19</sup> tends to show that despite increased permeability of the capillaries at the site of injury, substances pass more readily from the capillaries to the wounded area than in the reverse direction; after a short latent period, absorption from the burned area is slower than normal, and after eight hours the capillaries seem to have regained their normal permeability for colloid material. These workers believe that whatever symptoms develop during the secondary period are the result of infection rather than phenomena of the absorption of a specific burn toxin.

These findings, while of interest regarding absorption from the burned area, afford no substantial proof against the theory of toxin formation. We believe that the theory of toxin formation provides a firmer foundation than any other on which to rest the weight of our clinical impressions.

The patients who die in the first four to eight days after the burn probably primarily receive an overwhelming amount of the toxin, against which an ineffectual battle is waged. In the patients who seem to hold their own until shortly before death and then die rather abruptly after ten days or so, the initial amount of toxin absorbed probably acts as an antigen and sensitizes the patient; further absorption results in anaphylactic shock and death (Tuder<sup>23</sup>). Without doubt infection

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23. Tuder, T. J.: The Modern Treatment of Burns, *Internat. J. Surg.* **28**:282, 1915.

plays a considerable but little understood part in all patients who die from secondary toxic shock. Infection is invariably present, but its rôle is supplementary to the toxemia, and is not the *causis mortis per se*.

#### NATURE OF TOXIN

Strauss<sup>24</sup> recently collected sixteen different toxins described by various investigators. The nature or exact composition of the burn toxin is unknown, but it probably results from the breaking down of protein. Robertson and Boyd<sup>13</sup> described it as consisting of two parts, one thermostabile, diffusible and neurotoxic, and the other thermolabile, colloidal and necrotoxic, and stated that chemically it consists of primary and secondary proteoses.

#### PROGNOSIS OF BURNS

Patients at the extremes of life do not withstand burns as well as those in the more vigorous decades. One hundred and twenty-one of our two hundred and five cases occurred in patients between the ages of 20 and 50 years, with a mortality of 10 per cent. Sixty were under 20 years, with a mortality of 31 per cent, and twenty-three were above 50 years, with a mortality of 36 per cent. A fatal outcome is apt to follow burns of first degree involving two thirds of the body surface or burns of second degree affecting one third of the body surface in adults or one-seventh in children. All burns covering one third of the surface of the body are extremely serious (Christopher<sup>25</sup>).

#### ESTIMATION OF AREA INVOLVED

Berkow<sup>26</sup> has prepared the following table, which provides a method for reasonably accurate clinical estimation of the percentage of the surface of the skin involved.

Adult		Children Under 12 Years of Age	
Lower extremities and buttocks = 38%		12—child's age, plus 38 =	%
Upper extremities = 18%		12—child's age, plus 38 =	%
Trunk and neck = 38%		12—child's age, plus 6 =	%
Head = 6%			
Upper extremity: Hand = 2.5%			
Arm = 7.5%			
Lower extremity: Foot = 3.0%			
Leg = 6.0%			
Thigh = 9.5%			
Trunk: Anterior surface = 20.0%			
Posterior surface = 18.0%			

24. Strauss, A.: Burns and Their Treatment, *Ohio State M. J.* 28:101, 1932.  
 25. Christopher, F.: Present Status of Burn Therapy, *Am. J. Surg.* 5:61, 1928.  
 26. Berkow, S. G.: A Method of Estimating the Extensiveness of Lesions (Burns and Scalds) Based on Surface Area Proportions, *Arch. Surg.* 8:138 (Jan.) 1924.

## TREATMENT

The aims of any treatment are twofold: to save life and to preserve or restore function.

A cardinal principle in the treatment of all wounds, including burns, is the prevention of infection. Burn wounds are peculiar in that they are primarily sterile. In the fifth Book of Moses is found the following: "Everything that may abide the fire, ye shall make it go through the fire, and it shall be clean." These wounds likewise have been through the fire, and they are clean. No method, therefore, which introduces infection into a sterile field can be used except in flagrant disregard for every concept of medical science.

In our series of two hundred and five burns, two of every three deaths took place in the first twenty-four hours. Hence, the primary effort should be directed to saving the life of the patient, preservation of function being a secondary consideration. Early deaths, aside from the utterly hopeless cases, are probably due to mechanical causes incident to the great loss of blood plasma, dehydration of the tissues and the rapid concentration of the blood followed by the profound terminal shock. The use of tannic acid in precipitating the broken-down material and in sealing off the capillary bed at the outset is the best method of preventing loss of body fluids and heat. The only alternative method based on the same physiologic principles is the use of procaine hydrochloride-epinephrine packs introduced by Ravdin and Ferguson,<sup>27</sup> who applied 0.5 per cent procaine hydrochloride with 10 minims (0.6 cc.) of epinephrine to the ounce of solution to cause vasoconstriction and to seal off the capillary bed. At present Ravdin<sup>28</sup> favors tannic acid unless infection is feared, when he uses the procaine hydrochloride-epinephrine packs. Originally, a 2.5 per cent solution of tannic acid was used by Davidson, as he was afraid that a stronger concentration might result in too deep a caustic action. We use 10 per cent tannic acid in the effort to penetrate to the bottom of the burn and to secure at once a sterile scab, a sealed wound and a dry, noninfected and noninfective field. We have no fear that the stronger solution will damage living tissues. We spray 10 per cent tannic acid directly on the face without injury to the conjunctivae. The original idea was to coagulate only the top layers, but we endeavor to coagulate the entire thickness of the devitalized tissue, particularly that portion adjacent to the living tissues. The stronger concentrations have a greater

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27. Ravdin, I. S., and Ferguson, L. K.: The Early Treatment of Burns, *Ann. Surg.* **81**:439, 1925.

28. Ravdin, I. S.: Personal communication to the author.

power of penetration than the more dilute ones (Schuetz<sup>29</sup>). Deep penetration seals the capillary bed and by conservation of body fluids prevents concentration of the blood. Tannic acid precipitates the toxin-forming materials in situ, and holds them inert; bacteria are caught in the precipitated material and rendered harmless. A thick scab is produced which protects the underlying nerve endings and other tissues, and splints the entire injured area.

Complete excision of the dead and dying tissue under general anesthesia enjoyed considerable popularity at one time, but is now reserved for third degree burns, and the excision is followed by chemical sterilization of the raw area. As a primary procedure débridement is rarely used. Bancroft,<sup>30</sup> formerly an advocate of débridement, now prefers tannic acid. Shortly after a burn it is impossible to differentiate the areas of second and third degree burns, and needless sacrifice of healthy tissue is inevitable with any primary débridement.

The sodium bicarbonate bath treatment is based on the assumption that the proteases, which break down the protein material to form toxins, can act only in a faintly acid medium, and their activity is inhibited by a shift to the alkaline side (Weiner<sup>31</sup>). We have not employed this treatment, but it is commended for children.

The preceding four methods of treatment all deal directly with the burned tissue. Following its introduction in 1914 by Barthé de Sandfort,<sup>9</sup> paraffin wax has been widely used in Europe and in America. Sherman,<sup>32</sup> who has had wide experience with burns, stated in 1918: "The wax method does not contain any specific curative ingredients, but acts entirely mechanically allowing Nature to heal under conditions favorable for repair. The wax cotton dressing is a non-adhesive shell which excludes the air, maintaining a constant temperature, and forms a protective dressing to the proliferating tissues under the best physiologic conditions, allowing regeneration and restitution along natural lines." In a recent communication<sup>33</sup> he stated that in the neighborhood of sixty thousand burns have been thus treated and that the paraffin wax is used throughout the organization of the Carnegie Steel Company at present; he sees no reason to change the treatment. He believes that the two best treatments are paraffin wax and tannic acid.

29. Schuetz: Ueber oertlich secretionekommende und secretionen befoerdernde Wirkung, Arch. f. exper. Path. u. Pharmacol. **27**:202, 1890.

30. Bancroft, F. W., and Rogers, C. S.: Treatment of Cutaneous Burns. Ann. Surg. **84**:1, 1926.

31. Weiner, H.: Zentralbl. f. Physiol. **19**:349, 1905.

32. Sherman, W. O'N.: The Paraffin-Wax or Closed Method of Treatment of Burns, Surg., Gynec. & Obst. **26**:450, 1918.

33. Sherman, W. O'N.: Personal communication to the author.

## ROUTINE PROCEDURE IN TREATMENT OF BURNS

To treat patients with the promptness that the urgency demands, one must be prepared to deal with them on a moment's notice. We keep ready at all times steel frames fitted with electric lights and easily adjustable to any bed; sterile sheets, and a sterile gun of the type used for spraying insects. On all floors and wards tannic acid is kept in weighed amounts, with printed directions for preparing a 10 per cent solution. Morphine is given all patients with burns in the emergency room; the clothes are removed; the skin around the burned area is cleansed with ether, and if any grease has been applied as first aid to the burn this is gently washed off with ether; the loose skin is trimmed off, and the area is covered with sterile sheets before the patient is sent to the ward, where everything is in readiness for his reception, as a result of earlier notification. He is placed in bed on the sterile sheets; the cradle and lights are put in place, and the tannic acid spray is started. A hypodermoclysis of 1,000 cc. of saline solution is given promptly and is repeated every eight hours. A student nurse is assigned to special duty with each patient with burns on the ward during the first twenty-four or forty-eight hours, and she sprays the burned area every fifteen minutes for the first twelve hours, then once an hour for twelve hours, after which no spraying is done. The temperature under the cradle is kept at from 98 to 100 F. The cradles are sufficiently roomy to permit the patient to turn without knocking the injured area against the frame. The patient is given at least a full glass of water (about 300 cc.) every hour, making a total average intake of around 6,000 cc. in twenty-four hours. We believe that such thorough and energetic treatment in the early stage is fully justified. The use of a special nurse at first facilitates tanning to a greater depth with a coincident reduction of subsequent infection and sloughing, and saves nursing care in the later stages.

Daily estimations of the hemoglobin are made in every case. In moderate burns the readings may never be above normal, but in severe cases the hemoglobin may rise considerably. The rise of hemoglobin is the most accurate ready clinical method of estimating the concentration of the blood. Hemoglobin of 125 per cent indicates a precariously high concentration of blood, and hemoglobin of 140 per cent and over indicates a blood so concentrated that fatal collapse is imminent. This is a simple test, easily made and of great practical value, and it shows whether the patient is getting the fluids so essential at this time.

In extensive burns there are two stages wherein transfusion of blood is beneficial. In primary shock the transfusion is given usually



from ten to twenty hours after the burn and replaces the lost plasma or water-holding capacity of the blood at a time when the circulatory system is once more a closed system. In secondary toxic shock transfusion should be given after the first two or three days if the toxemia is increasing, as it does in one type. In those cases wherein death is considered due to further absorption of the toxin following initial sensitization, transfusion should be done at the first untoward sign; the exsanguination-transfusion of Robertson and Boyd<sup>34</sup> is probably the ideal procedure. They employed their method in children and saved several after the development of convulsions.

As a rule, we give a prophylactic dose of antitetanic serum. In the absence of infection, the patient is kept under the cradle and lights until all the membrane has peeled off and the delicate epithelium has become a little resistant. The presence of infection is evidenced after four or five days by one or more collections of fluid under the tanned membrane. Incisions are made to evacuate the fluid, and detached membrane is excised. The open areas are covered with paraffin gauze over which dressings moist with physiologic solution of sodium chloride or boric acid are laid. These dressings are not wet, but merely moist, and are applied at room temperature and not as hot compresses. So far as we could see, such dressings do not seem to cause any liberation of toxin through rehydration. No wet dressings of any kind should be applied until after the fourth day at the earliest. At each daily dressing more of the detached membrane is cut away. Firmly adherent membrane should not be disturbed. In third degree burns Lee<sup>35</sup> recommended cross-cut incisions through the membrane, dividing it into 2 inch (5 cm.) squares to permit drainage around the edges. Second degree, but not third degree, burns will epithelialize under the membrane.

With complete separation of the tanned membrane all burns of third degree present a granulating surface. Treatment is aimed toward destroying bacteria and stimulating granulations. For this purpose we apply over the granulating surface first several layers of paraffin gauze, then pads of surgical gauze wet with boric acid solution, and finally either rubber or sea sponges (fig. 2). These sponges are held in place by a pressure gauze bandage, and the whole dressing is kept wet constantly with the boric solution. This dressing promptly converts exuberant, pale, boggy granulations into firm, bright pink ones.

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34. Robertson, B., and Boyd, G.: *Toxemia of Severe Superficial Burns in Children*, *Am. J. Dis. Child.* **25**:163 (Feb.) 1923.

35. Lee, W. E.: *The Surgical Treatment of Burns*, *S. Clin. North America* **8**:901 (Aug.) 1928.

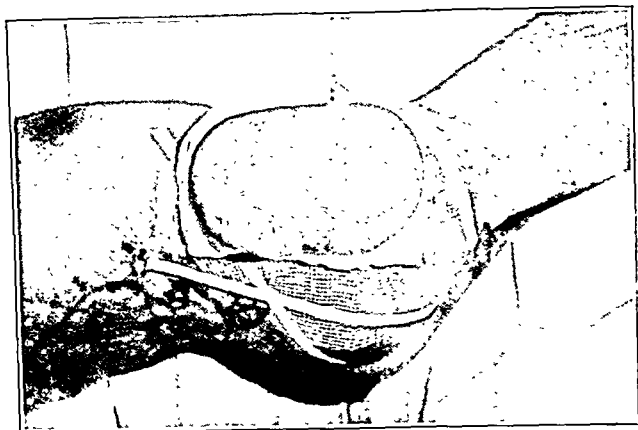


Fig. 2.—Dressing of granulating surface: application of surgical gauze over the paraffin gauze, with rubber sponge in place.

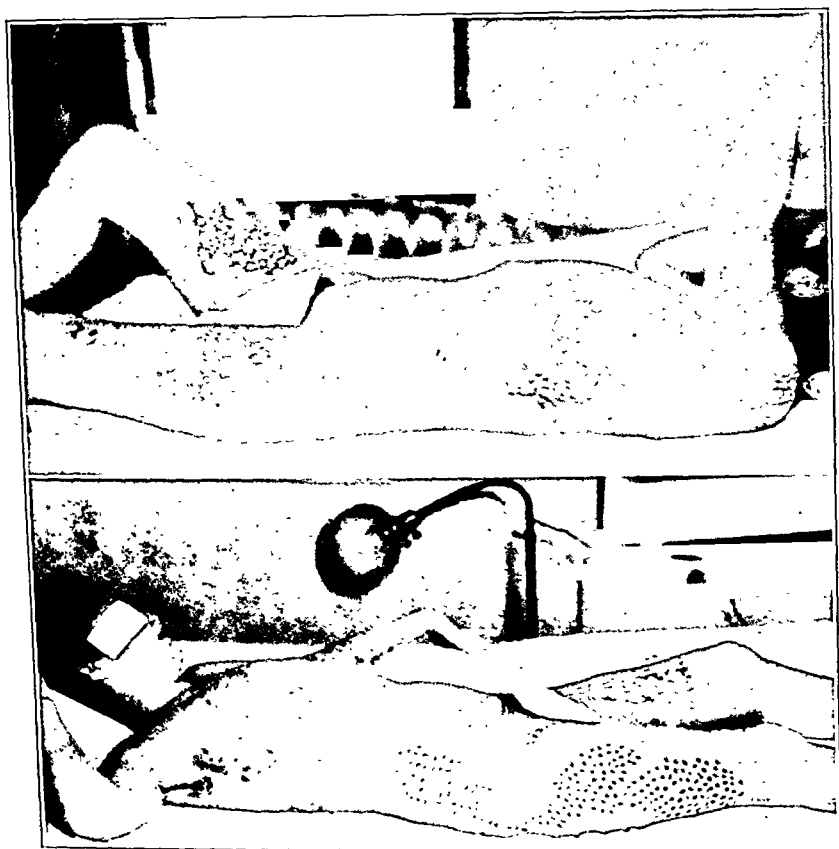


Fig. 3.—Second degree burns of left arm, entire chest, abdomen and anterior surface of both thighs from groins to knees. Third degree burns of left elbow, outer half of both breasts, right axilla, both groins and anterior surface of both thighs about halfway to knees. Tannic acid, 10 per cent spray. Reverdin pinch grafts seen on both thighs. Recovery. (Courtesy of Dr. A. O. Singleton.)

# Results of Treatment

Total number of cases.....	205	100
Total number of deaths.....	40	19.4
Deaths from primary shock.....	27	13.1%
Deaths from secondary toxic shock.....	13	6.3%
Total recoveries, all treatments.....	165	80.5
Total number of days in hospital, all recoveries.....	3,373	
Average hospitalization, all recovered cases.....	20.3 days	
Total days of toxemia, all recoveries, under all treatments.....	513	
Average duration of toxemia, all recoveries.....	3.1 days	
(Patient considered toxic as long as temperature persists above 100 F.)		
Race: White .....	146	71
Colored .....	59	29
Sex: White males .....	127	62
White females.....	19	9
Colored males .....	33	16
Colored females .....	26	13
Mortality		
Age, Years	No. of Cases	Primary Shock Secondary Shock
Under 1 .....	3	2 0
1 to 5.....	19	6 1
5 to 10.....	17	5 2
10 to 20.....	21	2 1
20 to 30.....	64	4 0
30 to 40.....	40	4 4
40 to 50.....	17	0 0
50 to 60.....	12	2 2
60 to 70.....	6	1 1
70 to 80.....	1	0 1
Age not given.....	5	1 1
Total.....	205	27 13
Patients treated with tannic acid.....		30
Recoveries .....		24
Deaths .....		6
Primary shock .....		3
Secondary toxic shock.....		3
Tannic acid recoveries.....		24
Total recoveries, other treatments.....		141
Total recoveries, all treatments.....		165
Number of second and third degree burns, tannic acid.....		20
Total number of days in hospital.....		914
Average hospitalization, recoveries, tannic acid treatment.....		45.7 days
Patients remaining over 100 days, tannic acid treatment .....		3
Total days, these cases .....		122
914 — 422		
Average hospitalization for ordinarily severe case: $\frac{17}{17} = 28.8$ days		
Number of second and third degree burns, other treatments.....		89
Total number days in hospital.....		2,107
Average hospitalization .....		23.6 days
Number of patients remaining over 100 days.....		2
Total days, these cases.....		240
2,107 — 240		
Average hospitalization for ordinarily severe case: $\frac{87}{87} = 21.3$		
Average duration of toxemia, tannic acid recoveries.....		4.9 days*
Average duration of toxemia, other treatment recoveries.....		4.1 days*
Fatal cases:		
Average hospitalization before death: Tannic acid treatment.....		17.6 days*
Other treatments .....		6.9 days*
Average duration of toxemia preceding death: Tannic acid treatment.....		11.6 days*
Other treatments .....		4.6 days*

## Results of Treatment—Continued

Etiology of Burns				
	Tannic Acid	Mortality	Other Treatments	Mortality
Fire.....	4	0	11	8
Clothes on fire.....	2	0	8	7
Scalds.....	9	2	39	5
Chemicals.....	2	1	13	0
Gasoline.....	9	2	37	7
Gas stoves.....	4	0	5	1
Alcohol.....	0	0	2	0
Oil.....	0	0	3	1
Electrical cases.....	0	0	4	0
Unknown.....	1	1	53	5
Totals.....	39	6	175	34

Mortality:	Per Cent
Tannic acid .....	20
Primary shock .....	10%
Secondary toxic shock.....	10%
Other treatments .....	19.4
Primary shock .....	13.7%
Secondary toxic shock.....	5.7%

Granulation tissue continues to form fibrous tissue at its base until covered with epithelium. Delayed epithelialization means excessive fibrosis, which (1) cuts off the blood supply and retards healing toward the center of the granulating area, (2) results in contracture deformities and loss of function, and (3) years later favors the development of cancer. Fibrosis can be kept at a minimum and healing greatly expedited by skin grafting. For all larger areas that do not contain epithelial rests from hair follicles and sweat glands, we prefer Reverdin pinch grafts (figs. 2 and 3), which will take in the presence of moderate infection. Exceptionally, we employ flap or pedicle grafts. Grafting should be done as soon as healthy granulations form, to prevent fibrosis.

### COMMENTS AND CONCLUSIONS

The number of patients treated with tannic acid is too small to compare satisfactorily with those dealt with by other forms of treatment, but a few things are shown in the accompanying tables. Of the thirty patients treated with tannic acid, three had a hospitalization period of over one hundred days each, while only two of the remaining hundred and seventy-five had so extended a sojourn. This indicates that the tannic acid saves more extensively burned patients than any other treatment, which is borne out by the mortality from primary shock, which under other forms of treatment is almost half again as great.

1. Tannic acid in a 10 per cent solution, used as a spray, is the best treatment for burns.

2. The tannic acid should be used with the intention of coagulating all the layers of devitalized tissue and sealing off the capillary bed at the earliest possible moment.

3. Every patient with burns should have a special nurse during the first forty-eight hours.

4. Daily estimations of the hemoglobin should be made as a routine measure until the hemoglobin reaches and maintains a normal level.

5. Transfusion of blood is often a life-saving measure.

6. Skin grafting is indicated at the earliest possible moment, especially over the flexor surfaces of the joints.

7. Amputation is a last resort, but let us recall the lines written many years ago:

'Tis the Chyrurgions praise, and height of art,  
Not to cut off, but to cure the vicious part.

Dr. John B. Carnett assisted in the preparation of this manuscript.

# IODIZED OIL IN BRONCHIECTASIS

INCLUDING A STUDY OF TWO CASES FOLLOWING LOBECTOMY

JOSEPH A. WEINBERG, M.D.

OMAHA

The use of iodized oil in bronchography and in the treatment of bronchiectasis has become widespread during the past few years. While it is generally considered that this procedure is not attended by serious consequences, there are possible dangers which have been described by several authors, among them Archibald and Brown<sup>1</sup> and Hedblom.<sup>2</sup> There has also been confusion on the question of how long the oil remains in the lung and how the lung disposes of it.

Recently I performed the operation of lobectomy on two patients with bronchiectasis (figs. 1 and 2) who had been treated with injections of iodized poppy seed oil 40 per cent for some time previous to operation. The lungs of both of these patients have been carefully examined for the presence and distribution of the oil. These data together with experimental work on animals are presented for the purpose of clarifying some of the points in controversy.

## INJECTION OF IODIZED OIL INTO HUMAN BRONCHIECTATIC LUNGS; EXAMINATION FOLLOWING LOBECTOMY

CASE 1.—In C. L., aged 25, symptoms began at the age of 17, following tonsillectomy. The sputum had been foul and profuse since the onset. The first treatment consisted of irrigations through a bronchoscope in 1925. Pneumothorax was induced in 1925, which relieved him for several months. He had been to New Mexico and Colorado for relief but with no success. Exeresis of the phrenic nerve, performed in 1929, gave him more relief than any previous therapy. However, the sputum had been offensive and profuse since the onset. When I first saw him he appeared undernourished, the skin had a cyanotic appearance and the face, neck and back showed severe acne. The fingers and toes were clubbed.

Injections of iodized oil were given on February 15 and 22, March 15 and April 5 and 29. During these injections the sputum became appreciably thicker and less in amount. However, the foul odor persisted and the patient continued to show evidence of sepsis.

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1. Archibald, E., and Brown, A. L.: Dangers of Introducing Iodized Oil into the Bronchial System, *J. A. M. A.* **88**:1310 (April 23) 1927.

2. Hedblom, C., in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 5, chap. 3, p. 32.

Bronchography following the injection of iodized oil revealed an extensive saccular bronchiectasis involving the entire left lower lobe. The bronchiectasis was apparently confined to this lobe.

In May, 1932, a left lower lobectomy was performed in several stages by actual cautery and ligation of the pedicle. The patient has been in excellent condition since the operation. There is no more foul sputum, the acne has disappeared and the skin is no longer cyanotic. A persisting bronchial fistula is gradually closing.

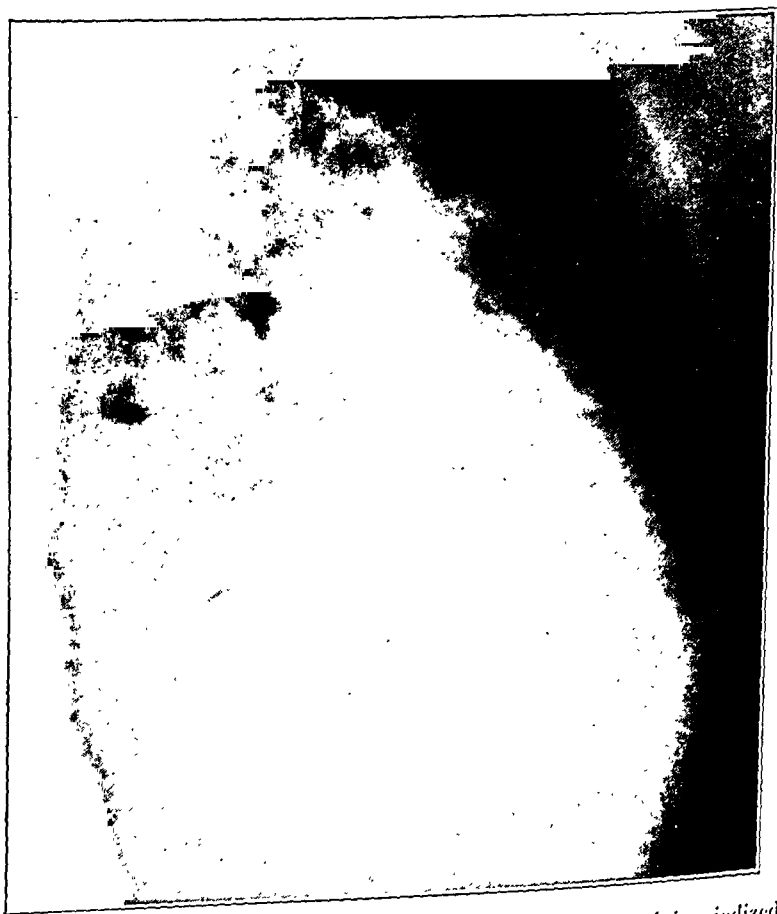


Fig. 1 (case 1).—Lateral view showing bronchiectatic sacs containing iodized oil.

A block of tissue was removed from the diseased lobe at the second stage of the operation, immediately before ligation of the pedicle. This was twenty-two days after the last injection.

Sections of material from the region of the secondary bronchi were stained with scharlach R and hematoxylin. The bronchial lumens were irregular, owing in part to the loss of typical bronchial wall structure and in part to an irregular hyperplasia of the mucosa. Both proximal and terminal bronchioles and the respiratory bronchioles were uniformly collapsed. The parenchyma was thickened in some areas, was replaced by connective tissue in others and showed a marked inflammatory reaction throughout. There were few areas in which alveoli could be recognized as such.

Several areas in each section revealed large accumulations of iodized oil within the bronchi and bronchioles (fig. 3). The bronchial mucosa was thickened and its cells contained oil droplets in a finely divided state. Droplets were also seen within the cartilage cells of the bronchial walls. In the parenchyma, the oil droplets were seen particularly within the large mononuclear cells of the alveolar walls. Apparently all of the various cells of the lung participated in the taking up of the oil.

CASE 2.—In H. L., aged 24, symptoms of cough and expectoration of purulent material developed at the age of 9. At the age of 14, following pneumonia, the

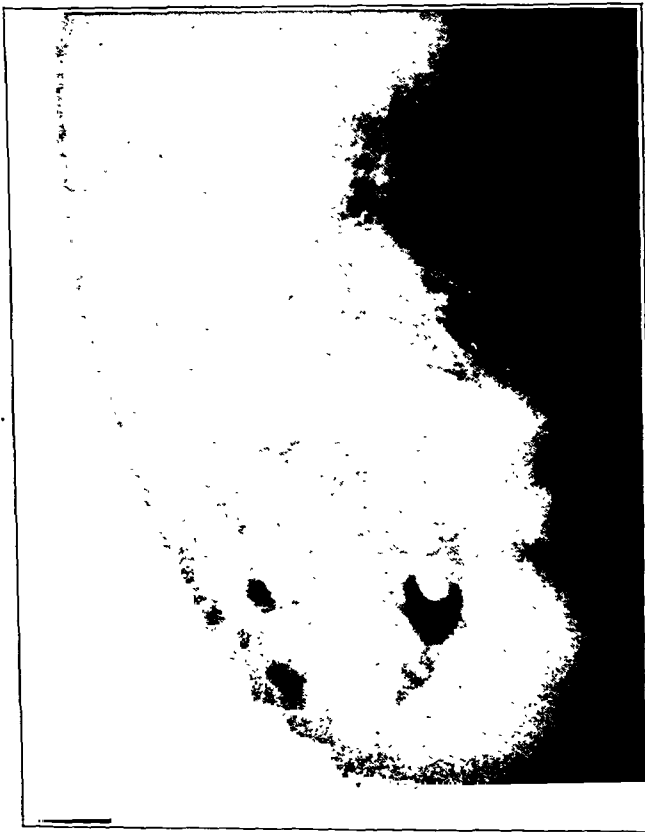


Fig. 2 (case 2).—Bronchiectasis of the left lower lobe with sac containing iodized oil.

expectoration became more profuse and foul. Since then the symptoms have become progressively more severe. In 1929, a complete left thoracoplasty was performed without relief. When first seen by me, in 1931, the patient showed a marked saccular bronchiectasis, apparently limited to the left lower lobe. Following exeresis of the phrenic nerve and injections of iodized oil the sputum was reduced from 1,500 cc. daily to 250 cc. daily. However, the sputum was very offensive, except during the first ten to fourteen days following each injection of iodized oil.

In June, 1932, a left lower lobectomy was performed by ligation of the pedicle and cauterization. Since then the patient has been free from symptoms of bronchiectasis.



A specimen of tissue was removed from the lower lobe just before ligation of the pedicle on June 13, eighty-three days after the last injection of iodized oil.

Microscopic study was made of sections stained with scharlach R and hematoxylin. The lung showed as the outstanding feature diffuse overgrowth of connective tissue, largely in the fibroblastic stage, with thickening and, in part, obliteration of the alveolar walls. There was a diffuse and, in some regions, dense accompanying infiltration of leukocytes. These were so dense in some regions as to suggest abscess formation. The bronchi were compressed and irregular, and showed fibrosis of their walls, with partial loss of mucosa and more peripheral structures of the wall.

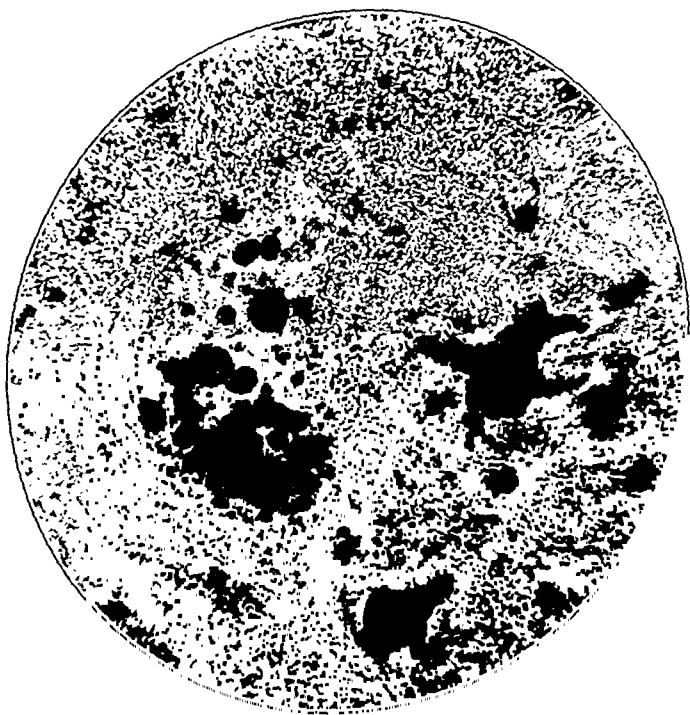


Fig. 3 (case 1).—Section of lung removed at the time of lobectomy, twenty-two days after the last of several injections of iodized oil. The oil is represented by the intensely black areas. The larger deposits of oil are within the bronchial lumens. Droplets of oil occur in the mucosal cells of the bronchi and in the cells of the fibrosed lung tissue. Note the inflammatory reaction and the absence of recognizable alveoli;  $\times 40$ .

As in the first case all types of cells in the section participated in taking up of oil droplets. The droplets were especially numerous in the large mononuclear cells in the alveolar walls and were present in large number in the lining cells of the bronchi and bronchioles. The distribution was not uniform, some areas showing a large number of cell inclusions of oil, others showing this phenomenon to a slight degree. Apparently some of the areas had failed to receive iodized oil by reason of incomplete injection into the bronchial tree. A few large extracellular drops of oil were seen in dense fibrous tissue (fig. 4).

These two specimens clearly demonstrate that the oil is taken up by all types of cells and is not limited to the large mononuclear phagocytes or related cells. From this observation it would appear that the phenomenon of ingestion of the fat particles is not essentially one of phagocytosis, but is rather the natural affinity of cells for fat.

It will be noted that the oil is present in large amounts eight-three days after injection into the bronchial tree. This is significant in pointing to the possible value of iodized oil as a therapeutic agent. It may be assumed that the oil which is present within the cells slowly liberates iodine and that the liberated iodine may have a beneficial



Fig. 4 (case 2).—Section of lung removed at the time of lobectomy, eighty-three days after the last of several injections of iodized oil. The intensely black areas represent deposits of oil. The accumulations are fewer and smaller than in case 2. All types of cells contained oil droplets;  $\times 40$ .

effect in lessening the degree of infection. It has been argued by opponents of iodized oil therapy in bronchiectasis that the substance cannot be of great value as it is not retained in the lung for a sufficient length of time to act in any great measure. The argument is not tenable against the observations in these cases.

An observation which aids in explaining the futility of iodized oil therapy in severe extensive bronchiectasis is the failure of the oil to enter many of the sacs. In these specimens the distribution is patchy after several injections of 20 cc. each. Even though the iodized oil

exerts a beneficial effect on those areas with which it comes in contact, the areas not receiving the oil are sufficient in number to continue the disease. This explanation is in harmony with clinical experience, in which it is observed that mild cylindric bronchiectasis responds to this form of therapy more satisfactorily than the severe saccular type.

A study of two bronchiectatic human lungs which had been given injections of iodized oil leads to the following conclusions:

1. Iodized oil may be retained in the lung for a period of at least eighty-three days following introduction of the oil into the bronchial tract.
2. Most of the cells found in the lung are capable of ingesting droplets of iodized oil.

#### EXPERIMENTS WITH IODIZED OIL IN ANIMALS: SERIES 1

Intratracheal injection of iodized oil was performed on a series of eleven guinea-pigs. Each animal was anesthetized with ether, the trachea exposed through a midline neck incision and 1 cc. of oil injected into the trachea by means of a 20 gage needle.

Guinea-pigs were killed on the third, fourth, seventh, eleventh, fourteenth and twenty-eighth day. In four of the animals death occurred on the thirty-ninth, forty-first, forty-fourth and fifty-fifth day.

At autopsy the lungs were removed by careful dissection, an attempt being made not to force out any of the iodized oil. Blocks of lung tissue were taken from uniform areas to include the hilus and periphery. Sudan III stains were made of frozen sections for oil demonstration, and hematoxylin and eosin stains were made of paraffin sections for more detailed study. The lung of a normal guinea-pig not given an injection of iodized oil was stained with the same technic for comparison. No oil was observed in the specimen from this lung.

Certain phases of these experiments have been previously reported by other workers, including Fried and Whitaker,<sup>3</sup> Brown,<sup>4</sup> Sato,<sup>5</sup> and Kotatsu.<sup>6</sup> However, it is felt that differences in interpretation and additional observations warrant a reconsideration.

EXPERIMENT 1.—A guinea-pig was killed on the third day after the injection. Gross examination of the lungs revealed a moderate congestion. A sudan III stained frozen section showed oil droplets collected in large number around the

3. Fried, B. M., and Whitaker, L. R.: *Intratracheal Injection of Iodized Oil*. Arch. Int. Med. **40**:726 (Nov.) 1927.

4. Brown, A. L.: *The Fate of Iodized Oil in the Lungs*, Surg., Gynec. & Obst. **46**:597 (May) 1928.

5. Sato, T.: *Histologic Changes in Bronchi After the Injection of Lipiodol*, Mitt. ii. allg. Path. u. path. Anat. **5**:183 (April) 1929.

6. Kotatsu, K.: *Changes in Pulmonary Tissues Following Intratracheal Introduction of Lipiodol*, Bull. Nav. M. A. Japan **18**:4 (May) 1929.

larger bronchi. Toward the periphery the oil was present in less amount, but it actually extended to the pleura. The droplets were present for the most part in the alveolar walls, and some were in the alveolar spaces. (It is possible that oil was present in the larger bronchi before sectioning and became dislodged with handling.)

Hematoxylin and eosin stain showed small areas of nonaerated alveoli. A moderate leukocytic infiltration was present in these areas, especially about the bronchi and bronchioles. These regions corresponded to the regions showing oil droplets in the sudan III sections. The lung was quite normal except for these patches. A few bronchioles showed a small amount of exudate in their lumens.



Fig. 5 (series 1, experiment 2).—Guinea-pig lung with area of atelectasis and inflammatory reaction four days after an injection of iodized oil. Note the purulent exudate within the bronchioles;  $\times 40$ .

Examination of the lungs in this animal revealed oil in the bronchial tree, alveolar spaces and alveolar walls. The injection of oil produced localized areas of atelectasis, these areas showing a mild inflammatory reaction on the third day after the injection.

EXPERIMENT 2.—A guinea-pig was killed on the fourth day after the injection. The lungs showed no gross abnormality. A sudan III stained section taken from near the main bronchus showed aggregations of oil droplets in the alveolar walls and to a less degree in the lumens of the alveoli. The droplets were grouped in clusters as though distributed about the bronchioles. A section from the periphery showed less infiltration of oil in the alveolar walls. In these sections the oil was in a much finer state of division and of much less quantity than in the animal killed on the third day.

Hematoxylin and eosin stain showed a rather marked inflammatory reaction throughout the specimen. The leukocytic infiltration was most marked about the blood vessels. There were also numerous areas of atelectasis with leukocytic infiltration. The bronchi and bronchioles contained an inflammatory exudate. The inflammation was less marked at the periphery than toward the hilus.

These specimens revealed much less oil than the specimens from the animal killed on the third day. Also the inflammatory reaction had reached a greater intensity. Thus, with the longer interval between the injection of iodized oil and the death of the animal, a more severe inflammation had developed in the areas of atelectasis, possibly as a

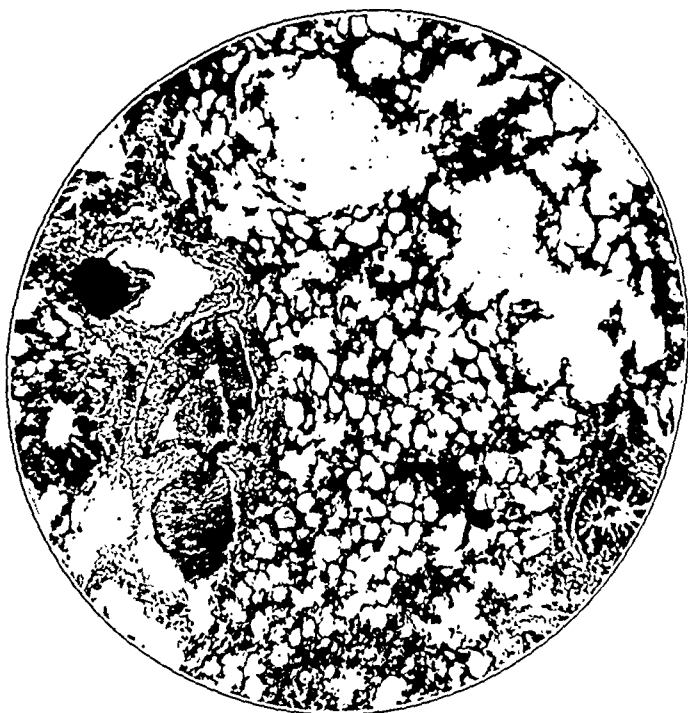


Fig. 6 (series 1, experiment 7).—Lung of a guinea-pig removed fourteen days after an injection of iodized oil. There was no evidence of atelectasis and little evidence of inflammation (compare with fig. 5);  $\times 40$ .

result of infection (fig. 5). One must also consider the possibility of irritation by the slowly released iodine, causing an inflammatory reaction.

EXPERIMENT 3.—A guinea-pig was killed on the seventh day after injection. It appeared healthy up to the time of death. Gross examination at autopsy revealed a moderate congestion.

Sudan III stain showed oil droplets in the alveolar walls, but they were fewer and smaller than in the animal killed on the fourth day. No oil droplets were seen in the bronchial tree or alveolar spaces.

A hematoxylin and eosin stained section, including the periphery of the lung, showed a rather massive atelectasis with an acute inflammatory reaction. There

was one small area of hemorrhage in the section. Most of the bronchioles in this area appeared to be collapsed and those remaining patent in and near the area showed a purulent exudate within their lumens.

EXPERIMENT 4.—A guinea-pig was killed on the eleventh day after the injection. It had been in good health up to the time of death. Gross examination showed congestion of both lungs. A sudan III stained section taken from midway between the hilus and the periphery of the left lower lobe showed oil present in fairly large droplets. No oil was observed in the alveolar spaces or lumens of the bronchial tree. This specimen showed more oil than was seen in the guinea-pig killed on the seventh day. It was confined for the most part to large areas of atelectasis.

Hematoxylin and eosin stain showed extensive areas of atelectasis, with a marked inflammatory reaction, especially in the areas of atelectasis. There was little evidence of inflammation in and about the bronchi and bronchioles.

The significant feature of this specimen was the retention of oil droplets in the collapsed areas. Apparently the atelectatic inactive lung tissue is less capable of ridding itself of oil droplets than is normal lung tissue.

In the animals killed on the fourth, seventh and eleventh days after the injection of oil the lungs showed a pronounced inflammatory reaction in the areas of atelectasis. This is of significance in suggesting the possibility of pneumonitis developing in the human lung following the diagnostic or therapeutic use of iodized oil.

EXPERIMENT 5.—A guinea-pig was killed on the fourteenth day after injection. It appeared healthy up to the time of death. Gross examination revealed no pathologic changes in the lungs.

Sudan III stain showed a few isolated oil droplets in an area of dense lung tissue. The droplets appeared to be in collapsed alveolar walls and not within the spaces. There was much less oil in this specimen than had been seen in any of the previously described animals, and all the oil droplets were in the areas of collapsed lung.

A hematoxylin and eosin stained section taken from the same area as that for the sudan III stain showed a definite leukocytic infiltration around the blood vessels. Congestion was present in the collapsed areas of lung. A section taken from an area near the hilus showed a much less pronounced inflammatory reaction.

EXPERIMENT 6.—A guinea-pig was killed on the fourteenth day after the injection. It appeared healthy up to the time of death. The lungs showed no pathologic changes on gross inspection.

Sudan III stain showed a fairly large distribution of oil, some in the lumens but more in the tissues. It was in a moderately finely divided state throughout the specimen.

A combination of sudan III and hematoxylin stains showed oil in the tissue surrounding the alveolar spaces.

Hematoxylin and eosin stain showed small areas of nonaerated lung with leukocytic infiltration, especially about the blood vessels. The changes were not so striking as those seen in the previously described animals, and were confined to much smaller areas.

EXPERIMENT 7.—A guinea-pig was killed on the twenty-eighth day after injection. It had been healthy up to the time of death. At autopsy the lungs appeared normal grossly.

A sudan III stained section taken from the upper part of the left lower lobe showed a number of groups of fine oil droplets in the alveolar walls. No oil was seen in the alveolar spaces. Occasional large drops were seen in the bronchial lumens.

Hematoxylin and eosin stain revealed a few scattered small areas of leukocytic infiltration, especially about the bronchi and bronchioles. There were no definite areas of atelectasis (fig. 6).

It may be inferred from experiments 5, 6 and 7 that the inflammation and atelectasis gradually subside after a period of two weeks (compare figs. 5 and 6).

EXPERIMENT 8.—A guinea-pig was found dead thirty-nine days after the injection of iodized oil. Gross examination revealed a massive pneumonia involving all lobes.

Scharlach R and hematoxylin stain showed only small areas of aerated lung, most of the tissue showing consolidation and acute inflammation. There was a large amount of oil deposited about the bronchi and to a less extent in the walls of more distant alveoli. One bronchus showed a large accumulation of oil in its lumen. The bronchi showed a marked leukocyte exudate. In one of the sections occasional small oil droplets were seen at the margin of the pleura. Throughout, the oil was intracellular and extracellular.

It is possible that in this animal an actual massive atelectasis occurred at the time of injection, thus accounting for the large amount of oil present at this late date. Such massive atelectasis could in time have produced an acute infection, which in turn could have resulted in the pneumonitis demonstrated at the time of death.

EXPERIMENT 9.—A guinea-pig died on the forty-first day after the injection of iodized oil.

Twenty-eight days after the injection the animal had been unable to use its hind extremities, probably because of an injury. Otherwise it appeared to be healthy. On the thirty-sixth day it was not as lively as previously, and on the forty-first day it was found dead. Gross examination at autopsy showed marked congestion of both lungs.

Sudan III stain showed slight evidence of oil in the consolidated portion of the section.

Hematoxylin and eosin stain showed a patchy pneumonia in the stage of red hepatization.

The findings in this experiment were quite different from those in experiment 8 in that the latter showed a complete lack of aeration in massive areas and the lung appeared atelectatic. The section revealed definite pneumonia.

EXPERIMENT 10.—A guinea-pig was found dead on the forty-fourth day after the injection. Autopsy revealed an extensive pneumonia, involving principally the left lower lobe.

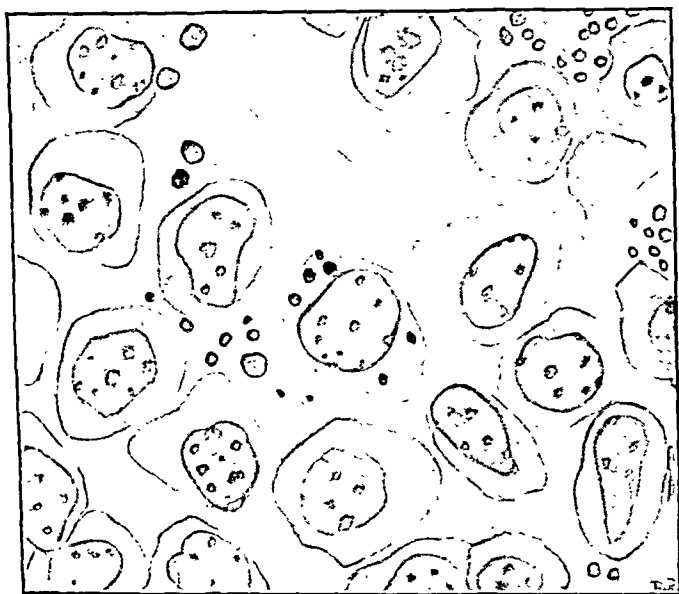


Fig. 7 (series 2, experiment 2).—Section from the middle lobe of a rabbit in which the lower lobe was ligated and iodized oil injected into the bronchial tree seven days later. The intracellular and extracellular particles of oil are shown in red;  $\times 5,000$





Scharlach R and hematoxylin stain showed extensive inflammation with leukocytic infiltration in the left lower lobe. A section from the right lower lobe showed scattered areas of inflammation. Most of the lung was aerated. The right lower lobe showed oil droplets within the alveolar walls. The left lower lobe showed the droplets for the most part within cells, but a few of them were extracellular. The droplets were few compared with previous experiments. There were no areas interpreted as definitely atelectatic.

This experiment also reveals a reaction quite different from that seen in experiment 8. In experiment 8 there was very little aerated lung, while in experiments 9 and 10 the lungs were well aerated and showed a widespread inflammatory reaction. The difference is explained by assuming that a massive atelectasis with subsequent pneumonitis occurred in experiment 8 as the result of plugging of a large bronchus with oil. In experiments 9 and 10 there is no evidence of such occurrence.

EXPERIMENT 11.—A guinea-pig was healthy until the fifty-third day after injection, when it was observed to be less lively. It was found dead on the fifty-fifth day. Gross examination showed a red-tinged fluid in both pleural cavities. Both lungs were markedly congested.

Sudan III stain showed oil droplets present in the tissues throughout the section. The oil was in a finely divided state. The lung was consolidated in the areas showing the greatest amount of oil.

Hematoxylin and eosin stain showed pneumonia in the stage of red hepatization.

In experiments 8, 9, 10 and 11 it is probable that the pneumonitis was related to the injection of iodized oil. In experiment 8, one must consider the possibility of atelectasis due to plugging of the bronchi with iodized oil, with subsequent infection imposed on the atelectatic areas. In experiments 9, 10 and 11 there was not sufficient atelectasis to infer that a massive atelectasis was present at the time of injection. If the iodized oil is to be considered a factor in causing the pneumonia found at autopsy, one may consider the possibility of multiple small areas of atelectasis becoming subsequently infected, and these in turn inducing pneumonia. It is interesting to note that all the animals which were allowed to live beyond the twenty-eighth day died with pathologic changes in the lungs. This was not due to an endemic occurrence of pneumonia, as other animals in the same room remained healthy. It is possible that the injection of oil is a factor in these deaths. It is not to be inferred from these experiments that there is the same danger of pneumonitis in man with the usual injection of from 5 to 20 cc. of iodized oil. An injection of 1 cc. in the guinea-pig would probably be equivalent to the injection of several hundred cubic centimeters in man.

As a result of the experiments described, several observations have been made, from which definite conclusions may be drawn:

1. The injection of iodized oil causes multiple areas of atelectasis, apparently owing to plugging of the bronchi and bronchioles.

2. These areas of atelectasis are always accompanied by an inflammatory reaction.

3. Oil droplets remain for a longer time in areas of atelectasis than they do in well aerated lung.

4. Oil droplets are quickly taken from the spaces by the tissues and may remain in the alveolar walls or may be carried for some distance, as noted in animals showing oil droplets in the pleura.

#### SERIES 2: EXPERIMENTS WITH LIGATED BRONCHUS AND INJECTION OF IODIZED OIL

A series of experiments were carried out on eight rabbits in which the main bronchus to the right lower lobe was ligated. By this means there resulted an almost complete necrosis of the ligated lobe, and partial atelectasis with multiple abscess formation in the upper and middle lobes on the same side. This stage of the experiment was originally performed by Lichtheim<sup>7</sup> in 1879 for the purpose of noting the effects of ligation of the bronchus. He found that those animals which lived beyond the twenty-four hour period became emaciated and died after from four to six weeks. At autopsy there were found extensive inflammation and necrosis of the ligated lobe together with dilatation and infection of the bronchial tree.

The rabbits were operated on under ethyl carbamate (urethane) anesthesia; a positive air pressure apparatus was used after the chest wall was opened. The bronchus to the left lower lobe was isolated and tightly ligated with plain or chromic O catgut. The chest wall was then closed and air was aspirated from the pleural cavity to restore low pressure.

The purpose of these experiments was to produce an infection in the lung simulating bronchiectasis. Following these experiments intratracheal injections of iodized oil were made in those animals surviving beyond the sixth day.

In addition to the results described by Lichtheim there was found a condition of more or less extensive abscess formation in lobes other than the ligated lobe. It is assumed that these abscesses were the result of "internal drainage," the phenomenon which has been described by Brunn and Faulkner.<sup>8</sup> The ligated lobe showed extensive necrosis beyond the degree seen in typical cases of bronchiectasis. The bronchi were dilated and were filled with purulent exudate. Conditions simulating bronchiectasis were also seen in the middle lobe, and to a less degree in the upper lobe on the side operated on. This was apparently the result of collapse together with infection through the bronchi.

7. Lichtheim: *Experiments Dealing with Pulmonary Atelectasis*, *Arch. f. exper. Path. u. Pharmakol.* **10**:54, 1879.

8. Brunn, H., and Faulkner, W. B., Jr.: *Intrabronchial Drainage*, *Surg., Gynec. & Obst.* **51**:115 (July) 1930.

EXPERIMENT 1.—A rabbit was operated on on July 14, 1931, under ethyl carbamate anesthesia. Under positive pressure breathing apparatus the right thoracic wall was opened, the right lower lobe ligated with chromic 0 catgut and the wall closed and sealed with celloidon. Air was withdrawn from the pleural cavity with an aspirating syringe. The rabbit died eighty-two hours after operation. Autopsy disclosed a small amount of fluid in the right pleural cavity, with the lung adherent to the diaphragm. The ligated lobe was about one fourth the normal size. The upper and middle lobes of the right lung showed extensive pneumonic involvement.

EXPERIMENT 2.—The same procedure was used as in experiment 1, with the exception that the right lower lobe was ligated with a plain 0 catgut. This type

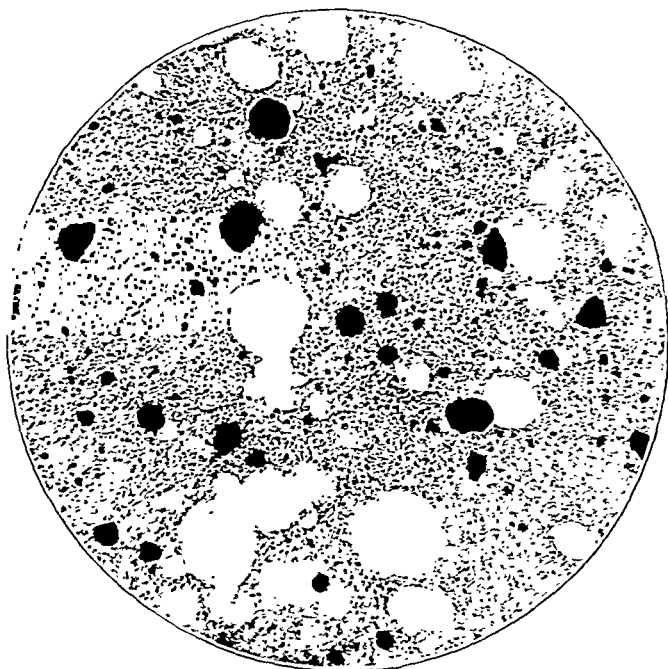


Fig. 8 (series 2, experiment 2).—Right upper lobe of a rabbit in which the right lower lobe was ligated and iodized oil injected into the bronchial tract seven days later. The animal was killed six days after the injection. The intensely black areas represent accumulations of oil;  $\times 40$ .

of ligature was used to allow earlier restoration of patency of the bronchus through dissolving of the suture, which was expected to occur within a few days following operation.

On July 24, seven days after operation, 2 cc. of iodized oil was injected by exposing the trachea and inserting a needle into its lumen.

On July 30, a roentgen examination was made. This showed slightly more oil in the right lung than in the left. The diaphragm was elevated on the right side.

The rabbit was killed with ether on July 30, thirteen days after the first operation.

At autopsy the left pleural cavity and lung appeared normal grossly. There was no gross evidence of congestion. The right hemithorax showed a yellow

fibrinopurulent exudate in the pleural cavity. The lower lobe was represented by a large abscess with a shell of recognizable lung parenchyma. The middle lobe was completely atelectatic with extensive abscess formation but not as extensive as in the lower lobe. The upper lobe was moderately shrunken and poorly aerated.

Sections were made of the upper, middle and lower lobes on the right side, and of the upper lobe on the left side. These sections were stained with scharlach R and hematoxylin. Also paraffin sections were stained with hematoxylin and eosin for more detailed study.

A hematoxylin and eosin stained section taken from the periphery of the right lower lobe showed a marked purulent pleuritis and complete necrosis of a

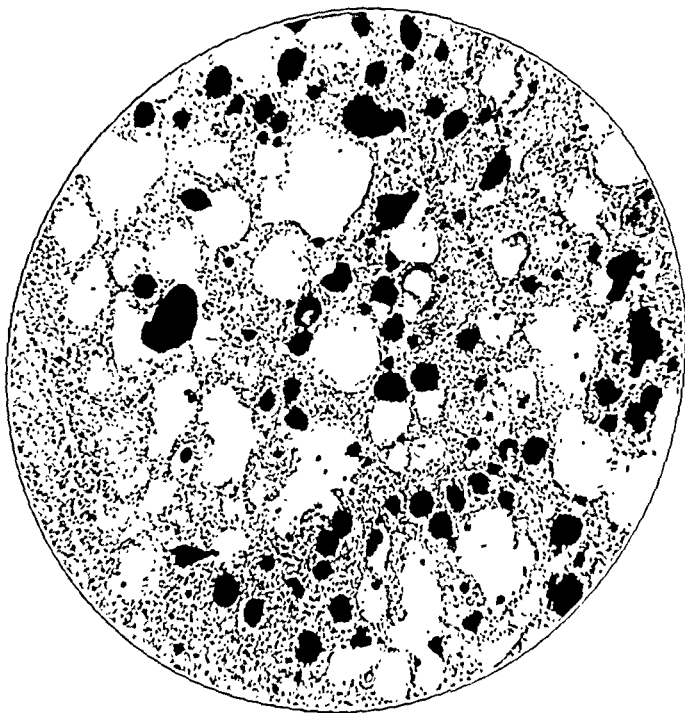


Fig. 9 (series 2, experiment 2).—Left upper lobe of a rabbit subjected to the procedure described for figure 8. The oil is retained in the same degree as in the right upper lobe (compare with figure 8);  $\times 40$ .

portion of the lung, with recognizable lung intervening between the two areas. The bronchi appeared degenerated and dilated.

Scharlach R and hematoxylin stain showed extensive atelectasis with occasional areas of fairly normal appearing lung. Large oil droplets were thickly scattered throughout the specimen, especially about a large bronchus. The oil droplets extended into the thickened pleura.

A hematoxylin and eosin stained section from the middle lobe showed organized pleuritis and local areas of atelectasis with leukocytic infiltration. The bronchi and bronchioles were dilated. The slide gave the impression of an atelectatic lung with mild infection of the bronchi and bronchioles.

Sudan III and hematoxylin stain showed a wide distribution of oil droplets of varying size extending into the thickened pleural wall, where they were contained within the endothelial cells.

Hematoxylin and eosin stain of the right upper lobe showed a rather well aerated lung with occasional areas of atelectasis. One bronchus in the specimen appeared to be markedly dilated and showed partial destruction of the wall with peribronchial inflammation.

A scharlach R and hematoxylin stained section from the right upper lobe showed large drops of oil throughout. The oil was present in the lumens of the bronchi, bronchioles and alveoli. The section also showed areas of atelectasis with an inflammatory exudate (fig. 8).

Scharlach R and hematoxylin stain of the left upper lobe showed a fairly extensive distribution of oil droplets in the lumens of the bronchioles and alveoli. The lung showed a mild inflammatory reaction with small areas of atelectasis (fig. 9).

EXPERIMENT 3.—A rabbit was operated on on July 24, 1931. The same technic with plain 0 catgut was used. The bronchus of the lower lobe was ligated.

The rabbit died six hours after operation. The lower right lobe was atelectatic and showed hemorrhage and congestion. The remaining portion of the right lung showed the same type of pathologic change but to a less degree.

EXPERIMENT 4.—An operation was performed on Sept. 16, 1931, under ethyl carbamate anesthesia. The bronchus of the lower lobe was ligated with plain 0 catgut.

Forty days after operation 2 cc. of iodized oil was injected into the trachea under ether anesthesia. The oil was introduced by means of an 18 gage needle inserted into the exposed trachea.

Fifty-six days after operation a roentgen examination showed much more oil in the right lung than in the left. The right diaphragm was displaced upward. The animal appeared to be in poor health. It was killed with ether on this date.

Gross examination showed collapse of the right lung, with an almost translucent fibrinous exudate in the pleural cavity. The left lung appeared to be enlarged. The right lower lobe, which had been ligated, was represented by a large abscess which was encapsulated and adherent to the diaphragm and parietal wall. A section taken from the capsule was recognizable as lung tissue. The middle lobe was atelectatic and contained numerous small abscesses. The upper right lobe was atelectatic and contained numerous small abscesses. The upper left lobe was atelectatic to a less degree and contained a few scattered abscesses. The left lung exuded a purulent material from the cut surface. This material seemed to come from the bronchi. Sections were taken from the right upper, middle and lower lobes and left upper lobe for examination.

A hematoxylin and eosin stained section from the right lower lobe showed a wall of fibrinous tissue and a central necrotic area. There was no recognizable lung tissue in this section.

Scharlach R and hematoxylin stain showed oil in a finely divided state in the necrotic area. Also oil was present within the large mononuclear cells in the thickened pleura. The presence of oil in the lobe indicated that the ligature around the bronchus had become loosened previous to the injection of iodized oil.

A hematoxylin and eosin stained section from the middle lobe disclosed a complete lack of aeration. The tissue showed fibrosis and leukocytic infiltration throughout. The bronchi were dilated and contained a purulent exudate. This section simulated advanced bronchiectasis to a remarkable degree.

Scharlach R and hematoxylin stain of the middle lobe revealed oil droplets in a very finely divided state. The droplets were seen more prominently about the bronchi and bronchioles, and were for the most part intracellular.

A hematoxylin and eosin stained section from the least inflamed part of the right upper lobe revealed a moderately congested lung with several small areas of atelectasis.

A scharlach R and hematoxylin stained section from the right upper lobe showed fairly large deposits of oil in alveolar spaces about the bronchi (fig. 10). In other areas the oil droplets were few and small. Oil was also present in the bronchi and bronchioles. This section, taken from a more condensed area than the hematoxylin and eosin stained section, showed a greater degree of atelectasis and a much greater degree of inflammatory reaction.

A hematoxylin and eosin stained section from the right lower lobe showed several minute abscesses of the lung. The bronchi showed an acute inflammatory reaction and were distended with leukocytic exudate. This infection was probably

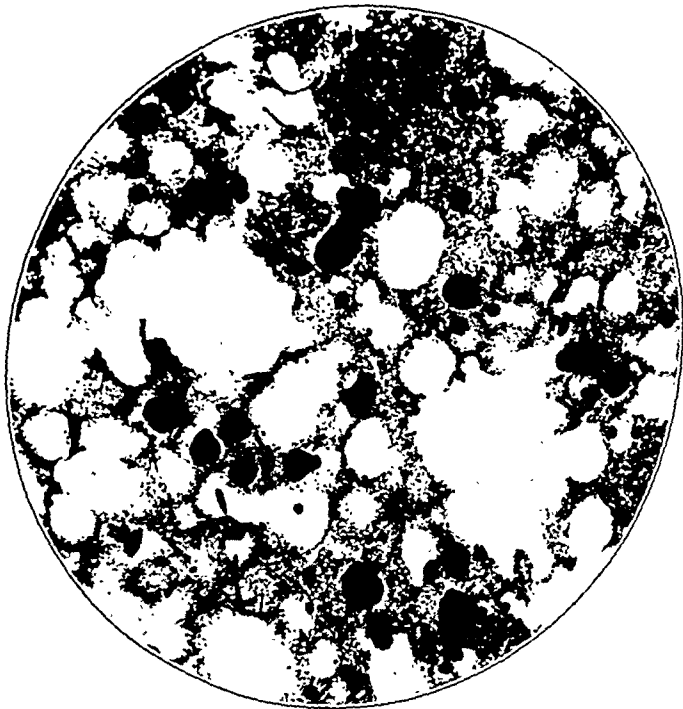


Fig. 10 (series 2, experiment 5).—Right upper lobe of a rabbit in which the right lower lobe was ligated and iodized oil injected into the bronchial tract forty days later. The animal was killed sixteen days after the injection. The intensely black areas represent deposits of iodized oil. Note the area of atelectasis in the upper part of the field;  $\times 40$ .

the result of "internal drainage" already referred to. Evidence of this was the fact that one of the larger abscesses had an infected bronchus in its center. Another abscess, of smaller diameter, had a bronchiole in its center.

Scharlach R and hematoxylin stain showed very little retained iodized oil (fig. 11). The droplets were rather widely separated from each other and were much smaller than those seen in the upper lobe of the right lung. Also they were smaller and fewer than those seen in the rabbit killed six days after the injection of iodized oil. It is assumed that at the beginning there was a more or less equal distribution of oil in the right and left lungs, and that in the time intervening between injection and death the oil had been taken up from the left

lung. The difference in the taking up of oil on the two sides may be explained by the fact that the active left lung was more capable of ridding itself of iodized oil than the fixed, more diseased right lung.

EXPERIMENT 5.—An operation was done on Sept. 16, 1931, under ethyl carbamate anesthesia. The usual technic was employed. During the anesthesia the stomach was distended with fluid. Air was not withdrawn from the right side of the chest following operation. The animal died twenty-four hours after operation. Death was probably due to distention of the stomach with fluid during the anesthetic and failure to withdraw air from the right pleural cavity. Autopsy disclosed collapse of the upper and middle lobes on the right side and partial collapse of the left lung. It is of interest that air remained in the ligated lobe to a

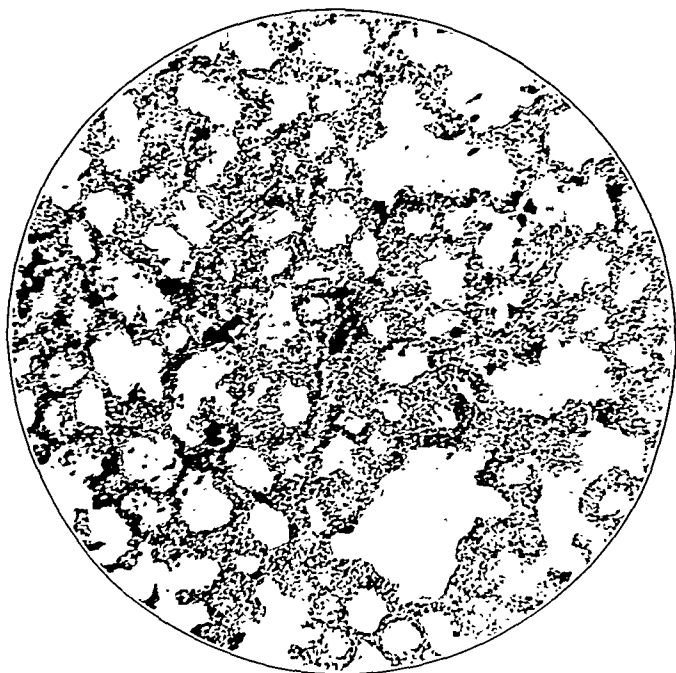


Fig. 11 (series 2, experiment 5).—Left upper lobe of a rabbit subjected to the procedure described in figure 10. Note the small amount of oil retained, compared with that retained in the adherent, more diseased right upper lobe (fig. 10). The droplets are much smaller and fewer than those in the left lung of a rabbit killed six days after an injection of iodized oil (fig. 9);  $\times 40$ .

greater degree than in the other lobes. Apparently insufficient time had elapsed for absorption of the retained air.

EXPERIMENT 6.—An operation was performed on a rabbit on Sept. 23, 1931. The usual technic was used. However, the insufflation was poorly performed and some of the air entered the stomach. The left lower lobe was torn in the ligation of the bronchus. Death occurred thirty-six hours after operation. An intense inflammatory reaction of the right lung was found at autopsy.

EXPERIMENT 7.—An operation was performed on Sept. 23, 1931. The usual technic was employed. The rabbit died seventy-two hours following operation.



Apparently all types of cells in the lung participate in the taking up of the oil droplets. The oil remains in the lung tissue for a period of at least eighty-three days following injection.

In bronchiectasis, with the usual injection of 20 cc. of iodized oil it is probable that many of the sacs in the diseased lobe fail to receive oil, according to the findings in the human lungs described here.

Experiments on animals show that injection of iodized oil into the bronchial tree results in multiple areas of atelectasis. The extent of atelectasis depends on the size of the lumen obstructed with oil. This condition usually subsides after a period of two weeks.

Several of the animals died from forty to fifty-two days after injection. All of these showed extensive pneumonitis. It is probable that the injection of an excessive amount of iodized oil was a factor in the development of the pneumonitis. This occurrence and the occurrence of atelectasis indicate that very small amounts of iodized oil should be used for diagnostic purpose in clinical work.

In experimental animals iodized oil is retained for a much longer period in the bronchiectatic lung than in the less diseased lung. This suggests an advantage in the use of iodized oil in the treatment of bronchiectasis in which prolonged contact is desired.

# SPONDYLOLISTHESIS AND PRESPONDYLOLISTHESIS

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NEW YORK

Spondylolisthesis was first described about seventy-five years ago. For a long time thereafter very few cases were recorded. Gradually, as the symptomatology became better known, more instances of this lesion were discovered. In the last two decades the subject has been studied in many quarters, and numerous reports, some of large series of cases, have appeared in the literature. At present many articles in English and foreign languages detailing the clinical aspects and the pathology are available. The exact etiology, however, has been a moot question. But increasing experience tends to confirm the opinion of recent observers that spondylolisthesis, whether coming on suddenly or appearing insidiously, is primarily the result of a congenital cleft in the laminae of the neural arch. As most of the cases are seen in adults, and none have ever been found in very young children (i. e., in the pre-adolescent age), one wonders about the time when slipping of the vertebra actually begins. There must be a variable period of months, or perhaps years, when the stage is set, so to speak, for the dislocation, but in which actual separation has not yet begun. This phase, which might properly be called prespondylolisthesis, is now receiving close attention and study.

While the majority of observers always felt that spondylolisthesis was due to a congenital lesion, there were some surgeons, I among them, who used to believe that at least some of the spondylolistheses were of traumatic origin. The latter sentiment was based entirely on the clinical history of a sudden onset following what was believed to be a competent injury. More deliberate and intensive study of the so-called traumatic, but otherwise typical, cases of spondylolisthesis has revealed, however, that there is rarely evidence of an injury that could be reasonably assumed to produce a fracture of the laminae. In addition, the x-ray pictures do not show any callus, which one would expect to see at the site of a fracture. Finally, at autopsies and in dissecting room investigations of uncomplicated cases, neither callus nor bony irregularities suggestive of a fracture have ever been seen. This does not mean that in terrifically severe accidents to the lower part of the back, in which there are multiple fractures, there may not also be a dislocation of a lumbar vertebra. Such cases have been reported

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recently by Dr. Hans Hellner. But in the ordinary case of spondylolisthesis the characteristic signs of a fracture are lacking. I now believe that while trauma is a most important contributory factor, it is not the essential cause in the etiology of spondylolisthesis.

A generation ago there were some surgeons who, because of roentgen appearances, believed that some cases of spondylolisthesis resulted from attenuation and elongation of the laminae which occurred in congenitally malformed vertebrae. In one or two instances I have, in the past, been inclined to such a view. Reexamination of one such case by more efficient roentgenography revealed the characteristic defect in the laminae. Moreover, in a personal interview with Dr. Willis, he told me that he had never seen, in his rather large series of anatomic specimens, any example of congenitally elongated laminae, nor has any other observer ever found such a lesion at autopsy. One can, therefore, exclude congenitally elongated laminae from the category of etiologic causes.

If one were to include in the title of spondylolisthesis all the types of dislocation of the lumbar vertebrae, one would be compelled to count among the etiologic causes such destructive diseases as tuberculosis and syphilis, especially in the tertiary stage, when, as in a Charcot spine, much disorganization of bony structures occurs, with the possibility of a dislocation of a lumbar vertebra. However, these displacements are manifestly part of a larger and more important pathologic change. In the characteristic case of spondylolisthesis, the forward dislocation of the vertebral body is the chief and predominant abnormality.

A bilateral cleft in the neural arch has been the constant anatomic defect found in every specimen of spondylolisthesis studied. In the examination of one thousand five hundred and twenty cadavers, Dr. Theodor Willis of Cleveland found seventy-nine instances of spondylolisthesis, and in every one of them there was a cleft through the laminae, which severed the posterior arch from the body of the vertebra. The cleft was bridged by fibrous tissue. There was no callus. There were often other congenital lesions, such as lack of fusion of the laminae at the spinous process, fusion of the spinous process with one lamina and not with the other, and so forth. Improved roentgenography now enables one to detect in the lateral view of almost every case the cleft between the articular processes, which separates the posterior arch from the vertebral body. The break in the osseous ring is always between the articular facets, and as a result the superior facets remain attached to the body and the inferior facets to the laminae.

The defect in the pedicles of a spondylolisthetic vertebra is of congenital origin and is readily explained on embryologic grounds. A

vertebra is believed to be formed from five centers of ossification, one for the body and two for each lateral mass. Of the latter, the anterior center forms the pedicle, including the superior articular facet, and the posterior center of ossification forms the lamina with the inferior articular facet. If these lateral centers of ossification fail to unite, there result a defect between the articular facets and a separation of the body from the posterior arch.

From the foregoing considerations it may be concluded that spondylolisthesis, or forward partial or total displacement of the body of a lumbar vertebra, is the result of a congenital cleft or split in the neural arch. The congenital osseous defect is the *sine qua non*. However, there are several important contributing etiologic factors that operate to initiate or to increase the dislocation.

#### ETIOLOGIC FACTORS

*Trauma.*—This plays a most important rôle in one of two ways in the production of spondylolisthesis. A sudden violence, as in jumping, a fall, lifting heavy weights, hyperextension of the spine in trying to avoid an accident or, as happened to one of my patients, in the fall of a heavy weight on the shoulders, may tear the fibrous attachment between the neural arch and the vertebral body and may at once displace the vertebral body forward. On the other hand, mild traumas often repeated, as in laborious work or sports, may stretch the fibrous tissue bridging the congenital cleft in the neural arch and may gradually dislocate the body of the vertebra.

*Abnormal Lordosis.*—This may favor spondylolisthesis. Cases of hollow back are seen in which the sacrum is nearly horizontal. A lateral x-ray picture shows that the lumbosacral plane is almost vertical, and that the last lumbar vertebra is in a position to slip off the sacrum. The weight of the trunk coming down on the bodies of the vertebrae tends to push the last lumbar downward. If there is a defect in the neural ring of the fourth or fifth lumbar vertebrae, the superincumbent weight would tend to displace its body.

*Convexity of the Superior Surface of the Sacrum.*—This condition also favors dislocation of the last lumbar vertebra. There are types of spondylolisthesis in which the upper surface of the sacrum is sharply convex, the front half of the superior surface sloping downward at an acute angle. In these cases the weight of the trunk would tend to force the last lumbar vertebra downward. It may be argued that in this group of spondylolisthesis the convexity of the superior surface of the sacrum is a sequel and not a cause of the dislocation. This is possibly so, but it would appear more logical to assume that, since it

is usual to find many congenital morphologic changes in the lumbosacral area, the malformation of the sacrum represents a congenital change.

*Obesity and Excessive Continuous Strain on the Pelvic Structures.*—As in pregnancy, these factors influence the appearance or the aggravation of spondylolisthesis. But all of these elements are only contributory and secondary to the basic cause, which is a congenital defect in the neural ring of the vertebra. Under normal conditions, that is, in the absence of a skeletal defect, the various contributory factors might be responsible for certain disabilities of the back, but they could not produce an actual dislocation of a lumbar vertebra.

Spondylolisthesis, though dependent on a congenital skeletal defect, is actually an acquired deformity, since the dislocation of the vertebrae occurs some time after birth. In fact, there is no record of this lesion in a patient under 10 years of age. The youngest patient I ever saw was 13 years old. The secondary or contributory factors that initiate the dislocation cannot come into play until the person begins to sit and to stand. In fact, spondylolisthesis is rarely seen in adolescence and usually does not occur until adult life, when the physical stresses become marked. In infancy and childhood the stresses are comparatively mild, and the tissues of the spine are elastic. A dislocation of a vertebra is, therefore, unlikely. In the adult, the elasticity of the spine is greatly reduced, and the differentiation between the osseous and the fibrous elements is clearly defined. An injury not severe enough to fracture a vertebra may stretch or tear the ligaments and other fibrous structures, and thus, in susceptible people, may cause a subluxation or dislocation. There is, therefore, in persons who are subjects for spondylolisthesis, a period in which there is as yet no dislocation, but in which one or more of the contributory factors are present and may at any time produce the deformity. The condition of the spine in this period may be called *prespondylolisthesis*.

*Prespondylolisthesis* was first recognized and described by Dr. Armitage Whitman. In 1924, at the annual convention of the American Orthopedic Association, Dr. Whitman reported the cases of a group of five patients who had two symptoms in common, namely, low backache and a marked lordosis. The lateral x-ray pictures in all of them showed that the lumbosacral angle was increased and the sacrum was almost horizontal. In three of the cases there was no other anatomic defect; in the other two there was a slight forward displacement of the last lumbar vertebra. Dr. Whitman believes that the unusual lordosis represents the initial stage of spondylolisthesis. One readily appreciates that in lordosis, especially when the sacrum is nearly horizontal, there appears to be no substantial support for the lumbar vertebrae and that

the lumbar spine is in a position favorable for dislocation. One sees many instances of extreme lordosis in men as well as in women, without symptoms of disability of the back or evidence of slipping of any of the lumbar vertebrae. The interlocking of the lumbar vertebrae and sacrum, both by numerous strong ligaments and by the articular bony processes makes dislocation unlikely unless some unusual circumstance is present. That unusual circumstance is a congenital cleft in the neural arch. Without such a defect in the neural arch, a dislocation of the vertebral body could not take place. The term *prespondylolisthesis*, which is an excellent one, should, in my judgment, be reserved for that condition of the spine in which, with or without lordosis, there is evidence of a defect in the bony wall of the neural arch of one of the lumbar vertebrae. Three cases of *prespondylolisthesis* have come under my observation. In one the lesion was discovered while fusion of the vertebrae was being performed for an unexplained chronic disabling backache. In the other two the diagnosis was made clinically by the finding of positive roentgen evidence of a defect in the neural arch of the last lumbar vertebra, and was confirmed at operation in one case. The patients were all males, only one of whom had an increase in the lumbosacral angle. In all of them a violence of sufficient force might have produced a real dislocation.

#### CASES OF PRESPONDYLOLISTHESIS

CASE 1.—John W., aged 33, was referred to me by Dr. M. J. Lippmann for a disabling backache. Two and a half years previously he fell down a flight of steps and struck his back against a post. Since then he had had pain in the lower part of his back which had interfered with his work and necessitated the wearing of a low back belt. The examination did not reveal any orthopedic, neurologic or other pathologic changes to account for the pain and disability. The patient was a tall, well built man. His back was symmetrical, and his posture satisfactory. There was no break in the anteroposterior physiologic curve of the spine. The motions of the spine were free in all directions. On arising from the flexed position, the patient complained of pain in the lumbosacral area. There was no tenderness to pressure over any part of the back. The x-ray films showed a normal alinement of the lumbar vertebrae and the sacrum. Had this been a so-called "compensation" case, one might have considered the claimant a malingerer. There could, however, be no doubt about the genuineness of the patient's complaint. A diagnosis of chronic sprain of the lumbosacral joint was made, and, since the symptoms had persisted for several years, fusion of the vertebrae was advised.

At operation I was surprised to find that the posterior arch of the fifth lumbar vertebra could be moved from a half to three-fourths of an inch (1.27 to 1.87 cm.), both laterally and vertically. The lesion, therefore, according to Dr. Willis' classification, was "a separate neural arch," due to a lack of fusion of the laminae to the vertebral body. At the site of the abnormal motion there was no roughened bone or callus. Hence, the lack of union of the posterior arch and the body could not be considered the result of a fracture. The lesion in the neural arch was evidently congenital. The injury probably caused a tear or stretching of the fibrous attach-

ment of the posterior arch to the front of the vertebra, with consequent abnormal mobility of the posterior arch and backache. In this type of case one can conceive that under unusual or prolonged physical strain the body of the fifth lumbar vertebra might slip down in front of the sacrum. The condition found in this patient's spine should properly be considered as a precursor of spondylolisthesis or a prespondylolisthesis. Incidentally, this patient made a perfect recovery. It is now two years since the operation. He does not wear any support, has no pain and is working regularly.



Fig. 1 (case 2).—Prespondylolisthesis. There is a marked lordosis. The sacrum is practically horizontal. There is no displacement of any of the vertebrae. At *a* is a defect in the laminae; at *b*, a superior articular facet continuous with the vertebral body articulating with the fourth lumbar vertebra; at *c*, an inferior articular facet joined to the lamina articulating with the sacrum.

CASE 2.—Oscar L., aged 41, came to my clinic at the Hospital for Joint Diseases because of increasing weakness and pain in both lower limbs. He was a carpenter, and had been able to do his work regularly. He had noticed, however, in the last few weeks, that he tired easily and was unable to walk more than half a mile without extreme fatigue. Twenty years ago he had fallen and hurt his back, but since then it had never been painful.

Examination showed a tall, well built man, who presented a markedly round, hollow back. There was an exaggerated lordosis. The gait was awkward. The

motions of the spine were somewhat restricted, but there was no tenderness to pressure over the lumbar or sacral regions. There were no motor or sensory disturbances. The knee and ankle reflexes were at times exaggerated. Lateral x-ray pictures (fig. 1) showed several important changes. The sacrum was practically horizontal. There was a marked vertical defect in the laminae of the fifth lumbar vertebra which separated the body from the posterior arch. The defect was at least an eighth of an inch (0.3 cm.) in width; it may be seen much more clearly in the original plate than in the reproduction. The x-ray film showed distinctly that the defect was between the superior and inferior articular facets of the fifth lumbar vertebra. The superior facets were attached to the body of the vertebra, while the inferior facets were continuous with the laminae and spinous processes. The alinement of the lumbar vertebrae and the sacrum was normal. A diagnosis of prespondylolisthesis was made. This was based primarily on the recognition of a defect in the neural arch of the fifth lumbar vertebra. The secondary signs were lordosis, a horizontal sacrum and the neurologic disturbances of weakness of the lower limbs and increased knee and ankle reflexes. Fusion of the vertebrae was advised.

At operation I found the same type of lesion as in case 1. The posterior arch could be moved laterally and in a vertical direction for at least a half an inch. Thus, the fifth lumbar vertebra had a separate neural arch. There was no evidence of any callus to suggest a previous fracture.

It may be fairly assumed that in this case had a fusion of the vertebrae not been performed in time, the body of the fifth lumbar vertebra would have slipped forward, giving rise to a partial or a total dislocation, or spondylolisthesis.

CASE 3.—Henry G., aged 64, came to the Hospital for Joint Diseases complaining of pain in the back of the right thigh. The pain had started four weeks previously. There was no history of disability of the back or previous illness or trauma. Examination revealed no abnormality of the back clinically. The lateral roentgenogram (fig. 2), however, disclosed a wide laminar defect in the fifth lumbar vertebra. This vertebra was in normal alinement with the fourth lumbar vertebra and the sacrum. The laminar defect was in the pedicle between the superior and inferior articular facets. The body of the fifth lumbar vertebra was wedge-shaped, and its inferior surface was concavoconvex, as is so often seen in a real dislocation. The sacrum was not horizontal, but its long axis was more oblique than normally and, as a consequence of this, there was some increase in the lumbosacral angle. The superior surface of the sacrum was convex. There was a marked reduction in the size of the intervertebral space or foramen between the fifth lumbar vertebra and the sacrum.

This case, from the roentgen evidence, is one of prespondylolisthesis. Whether a severe injury would have caused a dislocation is a matter for conjecture. It is unlike case 2, as there were no symptoms referable to the back. One may speculate on the reason for the comparative stability of the lumbosacral junction. Perhaps the most plausible explanation is that the laminar defect is only unilateral instead of bilateral, as in case 2.

*Comment.*—Cases 1, 2 and 3 are of special interest, because the diagnosis of prespondylolisthesis was established in the first case, and



in one of the other two, it was confirmed by operation. As many cases of spondylolisthesis are being seen, it becomes one's obligation to examine more carefully all patients who have backache, pains and weakness in the legs or a lordosis, and to see whether there is roentgen evidence of prespondylolisthesis. With the present-day improved technic in roentgenography, one has the opportunity of seeing clearly the morphology of the lumbosacral area and of recognizing skeletal defects. When the diagnosis of prespondylolisthesis may be reasonably suspected or is established by positive roentgen evidence, fusion of the vertebrae

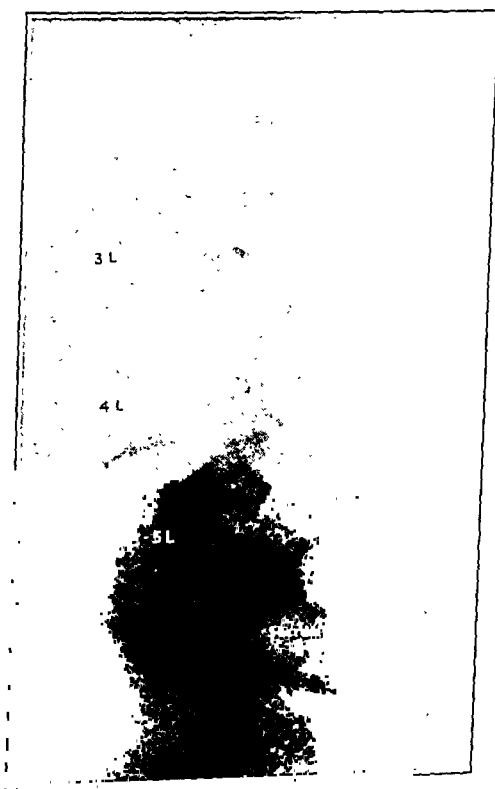


Fig. 2 (case 3).—Prespondylolisthesis. The arrow points to the laminar defect. Alinement of lumbar vertebrae and sacrum is normal. There is a moderate increase in the lumbosacral angle. The inferior surface of fifth lumbar vertebra is concavoconvex. The superior surface of the sacrum is convex.

should be performed to prevent later actual dislocation of the vertebral body.

#### CASES OF SPONDYLOLISTHESIS

Peculiarly enough, not all cases of spondylolisthesis show symptoms. If the condition of prespondylolisthesis gives rise to pain and disability, one would naturally suppose that an actual dislocation of such an important structure as the body of a vertebra, with the likelihood of pressure on the lumbosacral cord, would always produce marked symptoms. In

my present series of twelve cases, there were two in which the patients had no complaint referable to the lumbosacral region. The dislocation was discovered in a routine examination. The absence of symptoms can be accounted for on the supposition that the displacement took place so slowly that the tissues could accommodate themselves to the changed circumstances. In addition, neither patient had had any serious accident and never did any hard physical work as a result of which the lumbosacral area might have been subjected to strain.

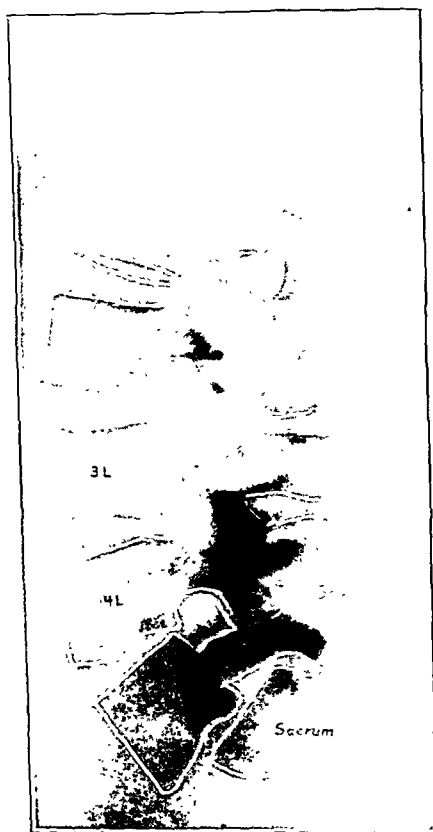


Fig. 3 (case 4).—Asymptomatic spondylolisthesis. The body of the fifth lumbar vertebra is displaced forward about three fourths of an inch. The sacrum is almost horizontal. The laminae of the fifth lumbar vertebrae appear elongated, but actually exhibit a defect and break in the neural arch; this is visible in the original film. The outlines of the vertebrae were deliberately emphasized by pencil, because the original film is rather light and would not have reproduced distinctly.

#### ASYMPTOMATIC SPONDYLOLISTHESIS

CASE 4.—Jacob H., aged 55, was referred to me for increasing deformity of the middorsal spine. The patient had locomotor ataxia, with all of the major symptoms, such as girdle pains, ataxic gait, pinpoint pupils, ataxia of the upper limbs, a positive Romberg sign. In the last two years a deformity of the middorsal

region was noticed. My examination revealed an extensive destructive lesion of the eighth, ninth and tenth dorsal vertebrae, which was presumably syphilitic. There was, however, in addition, a marked forward dislocation of the fifth lumbar vertebra. The lateral x-ray film (fig. 3) showed the body of the fifth lumbar vertebra displaced forward on the sacrum about three fourths of an inch. The laminae appeared elongated and unbroken, but in the original film the defect in the arch was distinctly discernible. There was a moderate increase in the lumbosacral angle. The long axis of the sacrum was more horizontal than in the normal state.

CASE 5.—Menitto D., a woman, aged 77, came to my clinic at the Hospital for Joint Diseases for pain in the right hip due, as the examination revealed, to osteoarthritis. The patient had no complaint whatever referable to her back. The



Fig. 4 (case 5).—Asymptomatic spondylolisthesis. There is subluxation of the fourth lumbar vertebra. The outlines of the vertebrae were purposely exaggerated to show the displacement of the fourth lumbar vertebra. The arrow points to a defect in the articular process, which was seen distinctly in the original film.

x-ray pictures showed a subluxation of the fourth lumbar vertebra. The lateral view (fig. 4) showed the body of the fourth lumbar vertebra displaced forward on that of the fifth vertebra, a distance of about three sixteenths of an inch (0.46 cm.). There was a distinct defect in the laminae, which separated the neural arch from the body.

#### SPONDYLOLISTHESIS WITH SUBJECTIVE SYMPTOMS

The subjective symptoms of spondylolisthesis vary in degree and are not at all in accord with the extent of the dislocation. Marked symptoms may be present when the dislocation is comparatively mild, and, vice versa, a severe dislocation may be accompanied by few com-

plaints and slight disability. The following cases are described in the order of the relative degree of displacement.

CASE 6.—Robert K.,<sup>1</sup> aged 30, was first seen on May 4, 1931. Ten days previously he fell through an opening in the floor, falling a distance of 6 feet. Subsequently he had had severe backache and difficulty in walking. Strapping of his back gave him considerable relief. The pain and stiffness of his back continued and were present when the patient was examined. The past history was interesting in that the patient had had five attacks of so-called lumbago during the past six years. These attacks, which consisted of stiffness of the back and awkwardness in walking, would last several days. They usually came on after a "cold" and had no relation to injury. Otherwise, the patient has led a very active life, indulging in golf, tennis and handball.

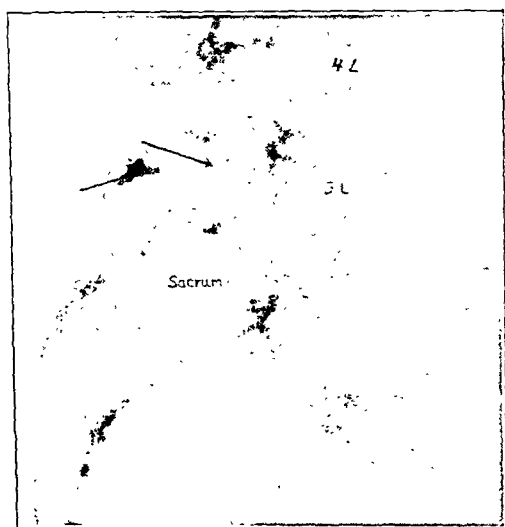


Fig. 5 (case 6).—Forward subluxation of the fifth lumbar vertebra. The arrows indicate the site of the laminar defect, which is evident in the original film.

Examination revealed a good posture and a symmetrical back, but a depression in the region of the spinous process of the fifth lumbar vertebra. There was slight limitation of lateral flexion of the spine. There was no tenderness to pressure over the lumbosacral area. The lateral x-ray picture showed a slight forward slipping of the fifth lumbar vertebra (fig. 5). The body of this vertebra was displaced about a fourth of an inch (0.64 cm.). There was a distinct defect in the laminae at the site of the articulations.

Whether the dislocation occurred during the recent fall or had been gradually coming on is difficult to answer. It is fair to assume that each "attack of lumbago" represented some degree of slipping, which was increased by the fall. The dislocation even now is mild and perhaps could have been prevented had the existence of a congenital defect in the neural arch been discovered sooner.

1. My associate, Dr. J. Buchman, allowed me to report this case

CASE 7.—Max L., aged 47, came to my clinic at the Hospital for Joint Diseases complaining of pain in the lower part of the back. In 1925, the patient fell off a 16 foot ladder, striking his back against a table. He had immediate severe pain in the lower part of the back. The pain was so marked that he was hospitalized for three weeks. Subsequently, he resumed part time work, but he had to wear a belt and received physical therapy. In 1930, he lifted a heavy case. During this act he felt something like a "crack" in the lower part of the back, and could not straighten up. Since this second accident the backache and disability had increased. The pain was of a gnawing character, radiating to the middle of the back. He had been unable to work.

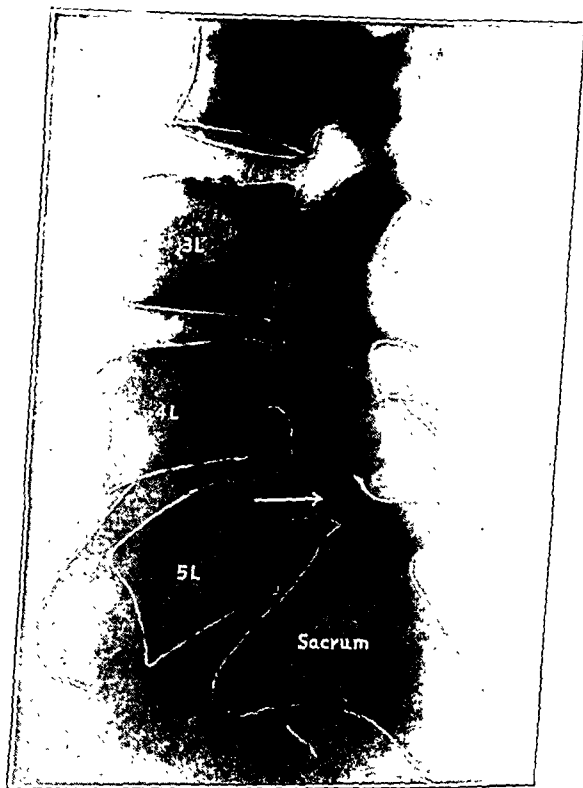


Fig. 6 (case 7).—Mild degree of spondylolisthesis. The subjective symptoms were marked and disabling. The original film was so light that the outlines of the vertebrae had to be emphasized for photographic reproduction. Note the laminar defect and displacement of the fifth lumbar vertebral body (arrow).

Examination showed a well built, overweight man. His back was symmetrical. There was no hollow above the sacrum. The spinal motions were slightly limited, and at the extreme of each motion the patient had considerable pain. There was marked tenderness to pressure at the lumbosacral junction. The lateral x-ray picture (fig. 6) showed a moderate subluxation of the body of the fifth lumbar vertebra. There was a wide defect in the pedicle, separating the articular facets. As the symptoms were of long standing and were disabling, fusion of the vertebrae was advised.

The patient was operated on on April 15, 1932, before a rather large audience of surgeons who were attending the clinical demonstrations during the week of

April 15 to 21, in commemoration of the twenty-fifth anniversary of the founding of the Hospital for Joint Diseases. After the skin incision was made, the spinous process of the fifth lumbar vertebra was identified and found to be abnormally movable. The posterior arches of the third, fourth and fifth lumbar and the first and second sacral segments were exposed. It was then easily demonstrable that the whole of the posterior arch of the fifth lumbar vertebra was abnormally movable in both the lateral and the vertical directions, owing manifestly to a bilateral break in the continuity of the neural arch. There were no fragments of bone, no callus and no bony spurs suggestive of a possible fracture.

This, then, is a case of spondylolisthesis of the fifth lumbar vertebra based on a congenital bilateral laminar cleft. As the symptoms came on after an injury, it is reasonable to assume that the trauma caused a

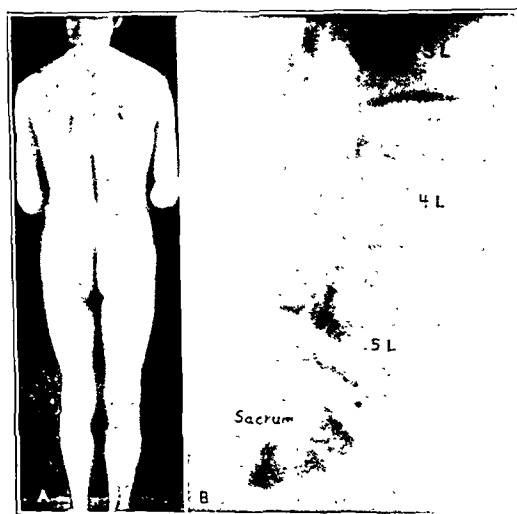


Fig. 7 (case 8).—*A*, note the deep groove in the lumbar region directly above the sacrum. *B*, lateral view, showing the forward displacement of the fifth lumbar vertebra.

tear of the fibrous bridge in the lamina. Subsequently, the weight of the trunk and the added strain of lifting a heavy case caused a forward displacement of the vertebral body. In this case trauma was a most important factor.

CASE 8.—Abraham P., aged 65, came to my clinic at the Hospital for Joint Diseases complaining of pain in the lower part of his back and in the left hip, radiating down the left thigh. The pain had come on ten months previously, after a fall in which he hurt his back. Examination showed that the patient walked awkwardly. He held his back stiff. There was a marked hollow above the sacrum (fig. 7) characteristic of spondylolisthesis. The lateral x-ray film (fig. 7 *B*) showed that the body of the fifth lumbar vertebra had slipped forward about a fourth of an inch. There was no unusual lordosis. The defect in the neural arch was not discernible.

It is manifestly impossible to state how long the dislocation had existed. Perhaps the displacement really took place only at the time of the alleged accident ten months previously. This would appear likely from the fact that the luxation was slight. Again one has the feeling that if the congenital defect and susceptibility to dislocation had been recognized earlier, effective preventive measures could have been applied.

CASE 9.—Margaret D., a colored woman, aged 45, was admitted to my clinic recently. She complained of pain in the lumbosacral area of the back, which radiated down the back of the right thigh and leg. The pain was remittent.



Fig. 8 (case 9).—*A*, note the marked depression above the sacrum, which is strongly suggestive of spondylolisthesis. *B*, note the forward displacement of the fourth lumbar vertebra.

When free from pain, she could work as hard as ever, but when the pain was present, laborious work was impossible. Three years previously the patient had fallen on her buttocks, injuring her right arm and the base of her spine. She had no trouble with her spine immediately after the accident, but three months later she began to have discomfort in the lower part of her back. This grew progressively worse. Prior to the injury she gave birth to two children and had no difficulty during either the pregnancies or the deliveries.

Examination showed an obese but well set up woman, who stood erect and walked without a limp. There was a marked groove in the middle of the lumbar region (fig. 8 *A*) strongly suggestive of a vertebral dislocation. The motions of the spine were abnormally free in all directions and were painless. There was slight tenderness to pressure in the lumbosacral hollow. The lateral roentgenogram

showed a forward displacement of the fourth lumbar vertebra on the fifth vertebra, to the extent of nearly half an inch (fig. 8*B*).

This case has several interesting features: The symptoms were brought on by a single severe injury. The clinical appearance is strongly suggestive of spondylolisthesis. The dislocation involved the fourth lumbar instead of the fifth lumbar vertebra. The mobility of the spine is unusually free. The disability is comparatively slight.

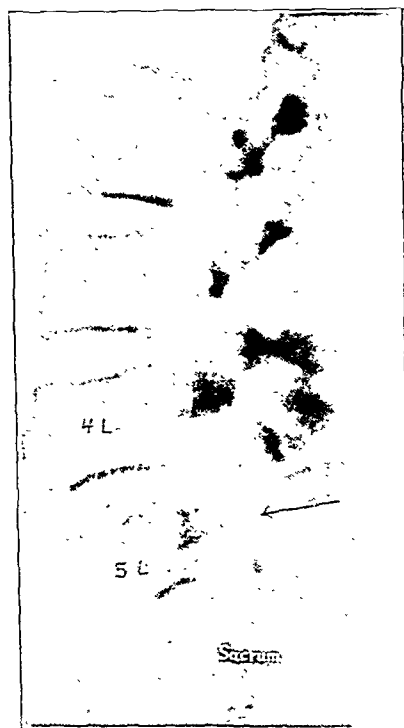


Fig. 9 (case 10).—Forward subluxation of the fifth lumbar vertebra. The laminar defect is very distinct (arrow). The front of the sacrum slopes downward, favoring dislocation. The body of the fifth lumbar vertebra is wedge-shaped; the lower surface is concave.

CASE 10.—Morris S. came to the outpatient department complaining of pain in the back of the right hip, which radiated down the back of the thigh to the knee. The discomfort had been present for six months. Examination showed a marked lordosis with a tilt of the trunk to the right. The lateral roentgenogram showed a moderate forward luxation of the fifth lumbar vertebra (fig. 9), with a very marked defect, about one eighth of an inch wide, occurring in the laminae. The superior surface of the sacrum was concavoconvex; the front half sloped downward. The inferior surface of the body of the fifth lumbar vertebra was concave, facilitating its descent from the sacrum.



CASE 11.—Sadie K.,<sup>2</sup> aged 28, came to the outpatient department of the Hospital for Joint Diseases complaining of backache. Examination revealed a marked lordosis and prominence of the upper sacral border. The lateral roentgenogram revealed a forward subluxation of the fifth lumbar vertebra (fig. 10). The body of the fifth lumbar vertebra is wedge-shaped and is displaced forward for about half its thickness. The lumbosacral angle is increased. The long axis of the sacrum makes an angle with the horizontal plane of hardly more than 25 degrees. The patient was provided with a plaster corset, which, however, did not relieve her pain. She refused to submit to the operation of fusion of the vertebrae.

CASE 12.—Albert P., aged 35, was admitted to the Hospital for Joint Diseases for an injury to his neck and head. While at his job as a structural iron worker, he was struck on the front of the left side of his neck and chest by the end of a



Fig. 10 (case 11).—Forward dislocation of the fifth lumbar vertebra. The body of the fifth lumbar vertebra is wedge-shaped and is displaced forward at least one-half inch. The sacrum is almost horizontal.

swinging steel girder, and was squeezed between this girder and another stationary one behind him. There is no history of the patient falling, doubling up or being struck in the lower part of his back. Almost immediately a huge crepitant swelling appeared in his neck. This gradually extended to the right side of the face. On admission to the hospital several hours after the accident, the patient looked very sick. He was coughing, and was dyspneic and moderately cyanotic. He was, however, thoroughly oriented and able to walk, and he did not complain of pain anywhere except in his throat and neck. At this time the patient was so desperately ill that the examination was limited to the throat, neck and chest. The emphysema threatened his life. X-ray films of the neck showed a fracture of the sixth and

2. This case is included in my series with the permission of Dr. Jahss.

seventh cervical vertebrae. The patient passed through a very stormy period; an infiltrating abscess developed, which burrowed down into the mediastinum and had to be drained by an extensive operation.

Five weeks after his admission to the hospital, the patient was well enough to get out of bed. Then a complete deliberate examination was made. This showed that the sacrum was very prominent. There was a marked groove in the mid-lumbar region strongly suggestive of spondylolisthesis. The patient was not aware of the hollow in his back and did not complain of backache. X-ray films showed the existence of spondylolisthesis. The lateral view (fig. 11) revealed a clear defect in the laminae of the last lumbar vertebra. The body of this vertebra was displaced forward at least half an inch. The lumbosacral angle was increased, and the long axis of the sacrum was almost horizontal. The intervertebral foramina

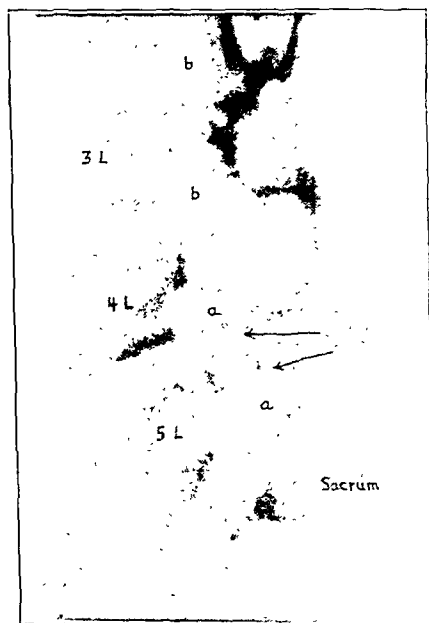


Fig. 11 (case 12).—Spondylolisthesis of the fifth lumbar vertebra. Note the marked defect in the lamina of the fifth lumbar vertebra. The body of this vertebra is displaced forward about one-half inch. The intervertebral foramina (*a*) between the fourth and fifth lumbar vertebrae and the fifth lumbar vertebra and the sacrum are smaller than those higher up (*b*). The sacrum is almost horizontal. The arrows point to a defect in the neural arch.

of the fourth and fifth lumbar vertebrae were decidedly smaller than those of the second and third lumbar vertebrae. The patient was not apprised of the finding of the dislocation.

Several months later the patient began to complain of lumbar backache, weakness and stiffness of the back and inability to lift objects. He had gained considerable weight. His symptoms increased, and finally fusion of the vertebrae was performed. When the laminae and spinous processes were exposed, the posterior arch of the fifth lumbar vertebra was found to be very loose and abnormally movable vertically and laterally. This was evidently due to a defect in the neural arch. No evidence of any callus was seen.

This was, then, a case of spondylolisthesis resulting from a "separate neural arch." As there was no direct blow on the lower part of the back, no symptoms referable to that part of the back at the time of the injury and no sign of any callus at the time of operation, a fracture of the laminae of the fifth lumbar vertebra may be excluded. Presumably, at the time of the injury the body was twisted, resulting in a stretching or tearing of the fibrous tissue. Subsequently, the increasing weight of the trunk caused a forward slipping of the body of the last lumbar vertebra or spondylolisthesis, giving rise to weakness and pain in the lower part of the back.

CASE 13.—Frances S., aged 35, consulted me in March, 1927, for pain in the lower part of her back. Five months previously, while bent over, putting on her shoes, she felt pain in the right sacro-iliac area. The pain persisted, and at times her trunk was deviated to one side. Examination showed that there was an increase in the posterior curve of the dorsal region, a corresponding increase in the lumbar hollow, and tenderness to pressure over both sacro-iliac joints. The x-ray pictures included the whole of the spine, the pelvis and the hips. They were made by Dr. Charles Gottlieb of New York. Both he and I noted that the x-ray films were negative. I made the diagnosis of subacute sprain of the sacro-iliac joints and treated the patient by conservative measures, which gave relief. The important fact is that at this time there was no evidence of spondylolisthesis. Unfortunately, I did not preserve the original film.

In February, 1931, nearly four years later, I was again consulted. One week previously the patient had fallen down a flight of steps, and since then had had pain and stiffness in the back and difficulty in walking. Examination showed an angular deformity of the spine at the dorsolumbar junction and a marked hollow at the lumbosacral joint. The spinal motions were markedly restricted, and there was tenderness to pressure over the dorsolumbar and lumbosacral regions. The x-ray pictures showed a compression fracture of the first lumbar vertebra and a forward subluxation of the fifth lumbar vertebra, or spondylolisthesis. The lateral film of the fifth lumbar vertebra (fig. 12) showed that the front of the body of the fifth lumbar vertebra was about one-half inch anterior to that of the sacrum. There was a gap of about half an inch in the substance of the laminae, with the spinous process of the fifth lumbar vertebrae in normal alignment with that of the sacrum.

This patient evidently had a congenital defect in the laminae of the fifth lumbar vertebra; the segments of the laminae were united by fibrous tissue. This fibrous union was torn by the violence of the recent fall. The forced flexion of the trunk during the fall caused not only a compression fracture of the first lumbar vertebra, but a forward dislocation of the body of the fifth lumbar vertebra.

The especially interesting feature of this case is that the patient had a congenital defect in the structure of the fifth lumbar vertebra, but up to the recent injury there was no dislocation. The fall was the immediate cause of the displacement, and in this sense the spondylolisthesis was traumatic. That the fall did not cause a fracture of the laminae and in that way bring about the spondylolisthesis was provid

by the lack of evidence of any callus at the defect in the laminae. This case resembles the others in the type of congenital defect in the laminae. Had this patient not had a severe injury, the dislocation might never have occurred.

CASE 14.—Helen S.,<sup>3</sup> aged 24, came to the Hospital for Joint Diseases complaining of tiredness and pain in the lower part of the back. The patient was a telephone operator, and she led a sedentary life. There was no known injury. The symptoms were of about four or five years' duration and had come on gradually. Examination showed a marked indentation in the back at the lumbosacral junction. The motions of the spine were restricted, and there was tenderness to pressure over the lumbosacral tissues.

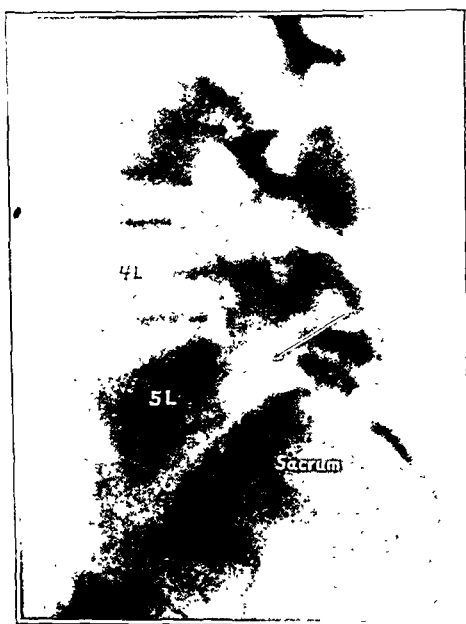


Fig. 12 (case 13).—Dislocation of the fifth lumbar vertebra. Note the extensive defect in the laminae of the fifth lumbar vertebra. The body of this vertebra is wedge-shaped and its inferior surface is concave, facilitating its descent from the sacrum. The long axis of the sacrum makes an angle of about 25 degrees with the horizontal plane. The spinous process of the fourth lumbar vertebra is displaced forward. The lower intervertebral lumbar foramina are reduced in size. The arrow indicates the laminar defect.

The lateral x-ray film (fig. 13) showed an almost complete dislocation of the body of the fifth lumbar vertebra. The superior surface of the sacrum was convex, with the front half sloping down abruptly. There was a rather wide defect or gap in the laminae of the fifth lumbar vertebra.

CASE 15.—Arthur H.,<sup>4</sup> aged 29, applied at the Hospital for Joint Diseases for relief of low backache of two years' duration. The onset had been gradual and

3. This case is included in my series with the permission of Dr. Harry Finkelstein.

4. Dr. Henry Milch allowed me to include this case in my series.

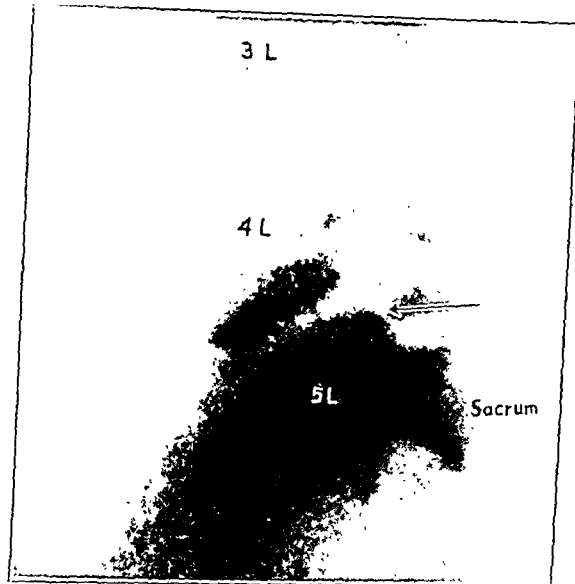


Fig. 13 (case 14).—Almost complete dislocation of the fifth lumbar vertebra. The laminar defect is wide (arrow). The upper surface of the sacrum is convex; the front half slopes down sharply. The body of fifth lumbar vertebra is wedge-shaped.



Fig. 14 (case 15).—Note the marked laminar defect (arrow). The body of the fifth lumbar vertebra is dislocated forward for about half its thickness. The upper surface of the sacrum is convex, and the front half slopes downward.

did not follow any injury. The patient stood with his body bent forward. There was a deep groove over the lumbar spine. The upper part of the sacrum was prominent. Flexion and lateral bending of the spine were free and painless. Extension was painful.

The lateral roentgenogram (fig. 14) showed a marked forward displacement of the body of the fifth lumbar vertebra on the sacrum. The posterior border of the body of the fifth lumbar vertebra was over the middle of the body of the upper

TABLE 1.—*Cases of Spondylolisthesis*

	Cases
Total.....	19
Males.....	12
Females.....	7
Trauma.....	11
Doubtful.....	2
No trauma.....	6

TABLE 2.—*Age Groups in Cases of Spondylolisthesis*

Age	Cases
10 to 20.....	1
20 to 30.....	4
30 to 40.....	7
40 to 50.....	2
50 to 60.....	2
60 to 80.....	3
Total.....	19

TABLE 3.—*Cases of Prespondylolisthesis*

	Cases
Total.....	3
Males.....	3
Laminal defect posteriorly.....	2
Of radiolysis.....	2
Increase in lumbosacral angle.....	2
Subjective symptoms.....	2
Asymptomatic.....	1
Ages 30 to 40.....	2
60 to 70.....	1

sacral segment. There was a marked defect in the laminae of the fifth lumbar vertebra. The superior surface of the sacrum was convex, the front third sloping sharply downward.

In previous communications I reported seven cases of spondylolisthesis which, added to the present twelve, make a total of nineteen cases in which there was a distinct forward displacement of one of the lumbar vertebrae. Of this series, the fifth lumbar vertebra was involved seventeen times and the fourth twice, which is about the proportion found by other observers. There were twelve male and seven female patients. This larger number of male over female patients, as represented in my figures, is confirmed by the statistics of some writers, but

not by those of others, who have found a slight predominance of spondylolisthesis among women. It is interesting, however, to observe that all recent students of this subject have found a large percentage of cases among men, in contradistinction to the older teachings that spondylolisthesis was seen only in women. Of the nineteen patients, one was 14 years old, eleven were in the age group from 20 to 40, and seven were more than 45. Trauma was a known factor in eleven of the nineteen cases. In two patients there was a doubtful history of injury, while in the rest there was no evidence of any outstanding trauma.

Tables 1, 2 and 3 combine the seven cases of spondylolisthesis previously recorded with the twelve in my present group.

#### PREVENTION OF SPONDYLOLISTHESIS

Cases of prespondylolisthesis are particularly interesting and important because through them one arrives at a means of preventing actual dislocation of a defective lumbar vertebra. One may readily believe that in cases of prespondylolisthesis, fusion of the vertebrae will prevent future dislocation of the fifth lumbar vertebra. In several of my group of spondylolistheses, in which the symptoms came on after an injury, the displacement of the vertebra was only slight and the dislocation, in the words of Max Hallner, was incipient. If one had recognized the bony defect prior to the alleged accident, it is conceivable that fusion of the vertebrae would have effected a stabilization that could resist an injury. It is at least a reasonable assumption, and one that should guide the policy of treatment.

#### SUMMARY

Prespondylolisthesis and spondylolisthesis are due to a congenital defect in the laminae of a lumbar vertebra, as a result of which the posterior arch of the vertebra is connected to the body only by fibrous tissue.

The diagnosis of prespondylolisthesis is made by finding a defect in the laminae of the lumbar vertebra without any displacement of the body. The clinical symptoms include pain and weakness of the back and a variable degree of disability.

A marked lordosis should make one suspect the existence of a prespondylolisthesis.

When the diagnosis of prespondylolisthesis is established, fusion of the vertebrae should be advised for the purpose of preventing an actual dislocation.

Spondylolisthesis is now being recognized with increasing frequency as an important cause of back disability.

The signs, symptoms and roentgen findings of spondylolisthesis vary in degree. The subjective symptoms are rarely in direct proportion to the degree of bony deformity.

Spondylolisthesis may exist for many years without causing symptoms or disability.

When symptoms are present, they may be relieved by external support of the back, or, in the more resistant cases, by fusion of the vertebrae.

In all cases in which operations were performed, the posterior arch was found to be abnormally movable and manifestly connected to the vertebral body only by fibrous tissue.

The patients operated on were relieved of their symptoms.



# CALCIFICATION OF THE TWORT MOUSE CARCINOMA (IN VIVO) BY MEANS OF VIOSTEROL

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AND

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Although great strides have been made in the knowledge concerning calcium metabolism during the last decade, many things connected with it remain unexplained. Studies have been greatly stimulated by the discovery of a concentrated form of vitamin D in irradiated ergosterol, the preparation of a potent parathyroid extract and the biologic action of ultraviolet rays. Careful chemical studies and admirable dietary regimens have added much to previous information. Even such a substance apparently so far removed from the problem as lead has, in the expert hands of Aub, his co-workers,<sup>1</sup> and others, yielded facts of much value in its relation to calcium metabolism. However, in the present study we are concerned only with the first mentioned agent, namely, viosterol. Summaries of the present knowledge on this subject may be found in readable form in Cantarow's monograph on calcium<sup>2</sup> and in Peters and Van Slyke's excellent textbook on quantitative clinical chemistry.<sup>3</sup>

It is well known that sufficient quantities of activated ergosterol will in time produce abnormal deposits of calcium in various parts of the animal body. Although the researches bearing on this are of recent date, the presence of such lesions is beyond dispute. Among the most

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Mead Johnson and Company of Evansville, Ind., contributed the viosterol.

From the Peiping Union Medical College and St. Luke's Hospital, San Francisco.

This work was done in the Department of Surgery, Yale University School of Medicine, New Haven, Conn.

Submitted to the Faculty of the Yale School of Medicine as partial requirement for the degree of Doctor of Medicine.

Such terms as viosterol, irradiated ergosterol and activated ergosterol are used interchangeably throughout the present article.

1. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: *Lead Poisoning*, Baltimore, Williams & Wilkins Company, 1926.

2. Cantarow, A.: *Calcium Metabolism and Calcium Therapy*, Philadelphia, Lea & Febiger, 1931.

3. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, vol. 1, Interpretations, Baltimore, Williams & Wilkins Company, 1931.

significant studies have been those of T. D. Spies,<sup>4</sup> Spies and Glover,<sup>5</sup> Kreitmair and Moll,<sup>6</sup> Smith and Elvove,<sup>7</sup> Hoyle,<sup>8</sup> Shohl, Goldblatt and Brown,<sup>9</sup> Simmonnet and Tanret,<sup>10</sup> Schiff,<sup>11</sup> Pfannenstiel,<sup>12</sup> Laas,<sup>13</sup> and von Brand and Holtz.<sup>14</sup>

Not only did Spies give findings in relation to the calcium deposits in various organs, but by means of viosterol he also produced the same process in tubercles. This accomplishment led us to believe that the same result might be secured in a neoplasm.

As regards the spontaneous calcific changes seen in human epithelial tumors, Ewing<sup>15</sup> stated that they are infrequent, usually associated with regressive processes, and that in rare instances they are concomitant in the viscera. Roussy<sup>16</sup> distinguished between the laying down of calcium in the stroma and in the neoplastic cells. In either case he noted the slow progress and sometimes even the disappearance of the growth.

Many chemical studies have been directed toward determining the calcium content of tumors. Most of the findings have been in agree-

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4. Spies, T. D.: Calcification of Tubercles, *Am. J. Path.* **6**:337, 1930; Calcification of Tubercles by Means of Irradiated Ergosterol in Experimental Chronic Tuberculosis, *Am. Rev. Tuberc.* **23**:169, 1931.

5. Spies, T. D., and Glover, E. C.: Renal Lesions with Retention of Nitrogenous Products Produced by Massive Doses of Irradiated Ergosterol, *Am. J. Path.* **6**:485, 1930.

6. Kreitmair, H., and Moll, T.: Hypervitaminose durch grosse Dosen Vitamin D, *München. med. Wchnschr.* **75**:637, 1928.

7. Smith, M. I., and Elvove, E.: Action of Irradiated Ergosterol in Rabbit, *Pub. Health Rep.* **44**:1245, 1929.

8. Hoyle, J. C.: Toxic Effects of Irradiated Ergosterol, *J. Pharmacol. & Exper. Therap.* **38**:271, 1930; **40**:351, 1930.

9. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: Pathologic Effects upon Rats of Excess Ergosterol, *J. Clin. Investigation* **8**:505, 1930.

10. Simmonnet, H., and Tanret, G.: Sur la toxicité pour les animaux de laboratoire de hautes doses d'ergosterol irradié, *Compt. rend. Acad. d. sc.* **190**:400, 1930.

11. Schiff, A.: Die durch Vigantol erzeugbaren Gefässwandveränderungen und ihre Rueckbildungsfähigkeit im Tierversuch, *Virchows Arch. f. path. Anat.* **278**:62, 1930.

12. Pfannenstiel, W.: Weitere Beobachtungen ueber Wirkungen bestrahlten Ergosterins im Tierversuch, *München. med. Wchnschr.* **75**:1113, 1928.

13. Laas, E.: Die Anfänge der Vigantolschädigung beim Kaninchen, *Virchows Arch. f. path. Anat.* **278**:346, 1930.

14. von Brand, T., and Holtz, F.: Beitrag zum Verlauf und zur Prognose der durch Überdosierung von Vitamin D Loesungen erzeugten Krankheit, *Ztschr. f. physiol. Chem.* **185**:217, 1929.

15. Ewing, James: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

16. Roussy, G.: *Le cancer, nouveau traité de médecine*, ed. 2, Paris, Masson et Cie, 1929, vol. 2, pt. 5.

ment with Beebe<sup>17</sup> and Clowes and Frisbie<sup>18</sup> in that rapid growth unaccompanied by necrosis indicates that there is a large amount of potassium and a small amount of calcium, but that the reverse is true in a slowly growing or necrotic oncoma.

Krehbiel<sup>19</sup> did not discover any significant variations in the blood serum calcium levels of people who bore either old or degenerated tumors. Theis and Benedict<sup>20</sup> demonstrated that the blood serum content of calcium was somewhat below normal in a fairly large percentage of patients with cancer.

Caspari and Ottensooser<sup>21</sup> observed some growth retardation of the Ehrlich mouse adenocarcinoma following the administration of irradiated ergosterol. However, they made no mention of the heightened calcific processes that were presumably present, and, consequently, one is justified in assuming that they did not make any observations relative to these interesting phenomena. Sumi<sup>22</sup> found that vitamin D did not materially influence the growth of a rat sarcoma.

#### PURPOSE

In view of various facts gleaned from the literature, it seemed worth while investigating whether viosterol might produce calcification of an actively growing carcinoma, and, if so, what effect it and the generalized deposition of calcium in the viscera might have on the biologic behavior of the tumor and its host.

#### EXPERIMENTAL MATERIALS AND METHODS

It was stated by the manufacturer that the viosterol was a sesame oil solution of irradiated ergosterol with a biologically-assayed antirachitic potency of 10,000 times that of cod liver oil, being designated as 10,000 CLO. In the first experiment it was deemed wise to use a weaker preparation, so that a dilution was made with sesame oil until a strength of 1,000 CLO was obtained. In the second study, a mixture of 2,000 CLO was given in the first ten injections, and one of 10,000 CLO was employed in the last nine administrations.

17. Beebe, S. P.: The Chemistry of Malignant Growths; The Inorganic Constituents of Tumors, *Am. J. Physiol.* **12**:167, 1904-1905.

18. Clowes, G. H. A., and Frisbie, W. S.: On Relationship Between Rate of Growth, Age, and Potassium and Calcium Content of Mouse Tumors (Adenocarcinoma Jensen), *Am. J. Physiol.* **14**:173, 1905.

19. Krehbiel, O.: Calcium Content of Blood with Special Reference to Cancer, *J. Cancer Research* **5**:199, 1920.

20. Theis, R. C., and Benedict, S. R.: Inorganic Constituents of Serum in Cancer, *J. Cancer Research* **8**:499, 1924.

21. Caspari, W., and Ottensooser, F.: Ueber den Einfluss der Kost auf das Wachstum von Impfgeschwülsten; Untersuchungen über das Vitamin D, *Ztschr. f. Krebsforsch.* **32**:74, 1930.

22. Sumi, M.: Influence of Vitamin D on Growth of Transplanted Sarcoma Gann **24**:239, 1930; abstr., *Am. J. Cancer* **15**:322, 1931.

The tumor was a transplantable mouse carcinoma secured from the Imperial Cancer Research Institute in London. The neoplasm was discovered by Dr. F. W. Twort, and his name has become attached to it. Murray<sup>23</sup> stated that it was an alveolar carcinoma, first found in the mammary region of a mouse, relatively slow-growing, successfully taking in from 70 to 100 per cent of the graftings, and metastasizing after a period of about eight weeks. Further notes regarding this tumor may be found in the reports of the Imperial Cancer Research Institute.<sup>24</sup>

In the first experiment were included, white, brown, black and gray mice in an attempt to observe any differences that might appear in various strains of animals. As none were noted, the second study was carried out entirely with albinos. Healthy young adults of both sexes were employed, and segregation was practiced in order to prevent pregnancies. Throughout the winter the mice were excellent experimental subjects, but in the summer great difficulty was had in avoiding epidemics of mouse typhoid (proved by repeated cultures) which swept the colony at intervals, causing wholesale deaths. After several such calamities, the reported investigations were carried on during the cold months in order to insure a sufficient longevity of the animals.

The diet consisted of oats, lettuce and milk. Excellent care was given to the animals, and their surroundings were strictly hygienic.

By means of a trochar and cannula (internal diameter of 1.5 mm.), small bits of carefully selected, viable tumor were transplanted into the subcutaneous tissue over the upper portion of the abdomen, approximately 2 cm. cephalad to the insertion point of the instrument through the skin. All grafting was completed within thirty minutes after killing the host of the parent growth, and the removed neoplasm was kept constantly moist with physiologic solution of sodium chloride. Cleanly cut pieces of tumor nearly as large as the bore of the cannula were used; thus all macerated and tiny bits were rejected. The percentage of "takes" ranged from 60 to 95.

At the beginning of the procedure, the instruments were thoroughly sterilized, but no attempt was made to antisepticize the skin of any animal except that from which the tumor came. No infections were observed. The probable rapid death of tumor cells exposed to germicidal agents would have required a drying of the skin before piercing it; and it is barely conceivable (but perhaps improbable) that the resulting prolongation of the autolytic processes within the excised carcinoma, due to the slight consequent loss of time, might have insignificantly lowered the number of successful grafts. Be that as it may, we found no need to elaborate our procedure.

In the early postinoculative period it was difficult to estimate the percentage of permanent "takes," for some transplants remained almost stationary for a time while others promptly increased in bulk and then either continued to enlarge or disappeared. Therefore, a few animals lost their tumors during the experimental period, but, in order that we might witness their general condition during life and examine their organs at death, they were not eliminated from the study.

An intraperitoneal method for the administration of the viosterol was employed. The evolution of this technic and the results secured (in addition to those on the tumor) constituted a special problem and have been incorporated in a separate article.<sup>25</sup> The procedure was merely the injection of viosterol into the peritoneal

23. Murray, J. A., Director Imperial Cancer Research Institute, London, personal communication.

24. Imperial Cancer Research Fund, London, rep. no. 4, 1911, and no. 5, 1912.

25. Spies, J. W., and Lyman, G. P.: The Intraperitoneal Administration of Viosterol in Mice, unpublished studies.

cavity through a hypodermic needle. The point of interest centered in to what extent, if any, the peritoneum of the mouse would absorb the vitamin D principle of irradiated ergosterol. Its efficacy in this direction was considerable, as was demonstrated by the calcification of organs which corresponded closely to the process shown by previous investigators as following the ingestion of suitable amounts of viosterol.

The injections of the sesame oil, certain samples of which contained activated ergosterol, were begun as soon as the permanency of the transplants seemed fairly assured, thus lengthening the time available for the inoculated substances to act and, by means of the utilization of young tumors, lessening the factor of spontaneous necrosis in the neoplastic cells.

The tissues were fixed in 70 per cent ethyl alcohol and then stained according to von Kossa's technic for the microscopic detection of calcium, and with hematoxylin and eosin for the study of cell structure.

The histologic presence of calcium deposits was the deciding factor as to whether negative or positive results had been obtained, but the general condition of the animals was observed as an indication of toxicity, and the growth of the tumor was noted as a matter of interest.

#### PLAN OF EXPERIMENTS

Illustrative details of two experiments are set forth. In the first of these a total of twenty-seven mice was employed. Eleven of these received viosterol in addition to the regular diet (table 1). A second group (experiment 1) contained nine mice, each of which was given unadulterated sesame oil plus the basal ration, thus serving as a control for the vehicle of the activated ergosterol (table 2). These two series received the same amount of sesame oil at each injection (table 4). A third lot (experiment 1) comprised seven animals which obtained nothing aside from the routine laboratory food (table 3).

At the beginning of the study each animal in experiment 1 bore a tumor. A few of these regressed during the period of observation. In order to care for the time factor, the span of life in the two control groups was made to parallel closely that in the viosterol series.

In experiment 2 there were thirty-five mice. The first group, consisting of fifteen tumor-bearing animals, received irradiated ergosterol and the customary diet. The second lot, comprising eleven tumor-bearing members, was given nothing in addition to the usual ration. The third series, containing nine tumor-free animals, was given injections of the same amount of viosterol as the first group. Thus the last two lots served as controls for the first. Data concerning experiment 2 are found in tables 5, 6, 7 and 8, respectively.

#### RESULTS

Tables 1 and 5 contain data which demonstrate that abnormal amounts of calcium were deposited in the experimental tumor and in the viscera of mice that were given intraperitoneal injections with viosterol over a period of from twenty-nine to sixty-one days. The longer the interval of time the greater was the intensity of calcification, but apparently it was more pronounced in the areas of recent necrosis.

this being especially noted in the carcinoma (figs. 2 and 3). However, one may not say from our studies whether the necrosis preceded or

TABLE 1.—*Experiment 1; Data on Viosterol Group*

Mouse	Tumor Present	Total Days*	No. of Doses	Microscopic Amount of Calcium	
				Tumors	Organs
1.....	No	25	7	.....	None
2.....	Yes	60	17	Moderate	Moderate
3.....	Yes	60	17	Moderate	Moderate
4.....	No	45	12	.....	Moderate
5.....	Yes	49	13	Moderate	Moderate
6.....	Yes	29	8	Moderate	Moderate
7.....	Yes	61	17	Moderate	Moderate
8.....	Yes	45	12	Moderate	Moderate
9.....	Yes	26	8	Slight	None
10.....	Yes	58	17	Moderate	Moderate
11.....	No	31	9	.....	Moderate

\* Total days from the time of the first injection of viosterol to death.

The administration of viosterol began ten days after the grafting of the tumor.

There were eleven mice. Eight had tumors, all of which showed calcification. Eight mice revealed the same process in the lung, stomach, kidney and aorta.

TABLE 2.—*Experiment 1; Data on Sesame Oil Group (Controls)*

Mouse	Tumor Present	Total Days*	No. of Doses	Microscopic Amount of Calcium	
				Tumors	Organs
1.....	Yes	45	12	None	None
2.....	No	22	6	.....	None
3.....	Yes	41	11	None	None
4.....	No	41	11	.....	None
5.....	Yes	61	17	None	None
6.....	Yes	61	17	None	None
7.....	Yes	68	17	None	None
8.....	No	53	15	.....	None
9.....	No	35	10	.....	None

\* Total days from the time of the first injection of sesame oil.

The administration of sesame oil began ten days after the grafting of the tumor.

There were nine mice. Five had tumors. No calcification was seen in either the tumors or the organs.

TABLE 3.—*Experiment 1; Data on Group into Which No Injections Were Made (Controls)*

Mouse	Tumor Present	Total Days*	Microscopic Amount of Calcium	
			Tumors	Organs
1.....	Yes	40	None	None
2.....	No	61	.....	None
3.....	Yes	41	None	None
4.....	Yes	26	None	None
5.....	Yes	58	None	None
6.....	Yes	58	None	None
7.....	Yes	58	None	None

\* Total days from the time of beginning of the injections in groups 1 and 2.

The tumor was grafted on the same date as in the other groups of experiment 1.

There were seven mice. Six had tumors. No calcification was seen in either the tumors or the organs.

was caused by the deposit of calcium. A similar process, of lesser extent perhaps, was seen in the pulmonary metastases (fig. 4).

The evidence amassed in tables 3 and 6 reveals that those mice which were given only the usual diet did not show calcium by the von

TABLE 4.—Experiment 1; Dosage

Number of Doses	Amount* Each Dose, Cc.	Total Dosage, Cc.	Period of Dosage, Days
1,000 CLO			
1.....	0.10	0.10	1
2.....	0.10	0.20	5
3.....	0.10	0.30	8
4.....	0.10	0.40	12
5.....	0.10	0.50	15
6.....	0.10	0.60	19
7.....	0.10	0.70	22
8.....	0.10	0.80	26
9.....	0.10	0.90	31
10.....	0.10	1.00	36
11.....	0.10	1.10	40
12.....	0.10	1.20	43
13.....	0.133	1.333	47
14.....	0.133	1.466	50
15.....	0.133	1.599	54
16.....	0.133	1.732	57
17.....	0.133	1.865	61

\* In terms of a sesame oil solution of irradiated ergosterol having a biologically-assayed antirachitic potency of 1,000 times that of cod liver oil.

TABLE 5.—Experiment 2; Data on Viosterol Group

Mouse	Tumor Present	Total Days*	No. of Doses	Microscopic Amount of Calcium	
				Tumors	Organs
1.....	Yes	43	14	Moderate	Large
2.....	No	49	17	.....	Large
3.....	No	49	17	.....	Large
4.....	Yes	50	18	Large	Large
5.....	Yes	50	18	Large	Large
6.....	Yes	50	18	Large	Large
7.....	Yes	50	18	Large	Large
8.....	Yes	51	18	Moderate	Large
9.....	Yes	51	18	Large	Large
10.....	Yes	52	19	Large	Large
11.....	Yes	52	19	Large	Large
12.....	Yes	52	19	Large	Large
13.....	Yes	52	19	Large	Large
14.....	Yes	52	19	Large	Large
15.....	Yes	52	19	Large	Large

\* Total days from the time of the first injection of viosterol to death.  
The administration of viosterol began ten days after the grafting of the tumor.  
There were fifteen mice. All showed calcification of lung, stomach, kidney and aorta.  
Thirteen of the mice had tumors, each of which revealed calcification.

TABLE 6.—Experiment 2; Data on Group into Which No Injections Were made

Mouse	Tumor Present	Total Days*	Microscopic Amount of Calcium	
			Tumors	Organs*
1.....	Yes	43	None	None
2.....	Yes	43	None	None
3.....	No	46	.....	None
4.....	Yes	49	Very slight	None
5.....	No	49	.....	None
6.....	Yes	49	None	None
7.....	Yes	49	None	None
8.....	Yes	49	Very slight	None
9.....	Yes	51	None	None
10.....	No	51	.....	None*
11.....	Yes	51	None	.....

\* Total days lived as dated from the time of the first injection of viosterol in previous group (table 5). The mice represented by tables 5 and 6 received tumor grafts on the 10th day.  
There were eleven mice. Eight had tumors, of which two showed very slight calcification.

Kossa histologic method except to a minor degree in two instances, these being limited to the tumor and probably due to viosterol secured by coprophagy. Necrosis of the neoplasms seemed as marked in the control animals (fig. 1) as in those which had been given large amounts of viosterol, thus evincing that so far as the carcinoma was concerned the death of the tissues probably preceded the laying down of the

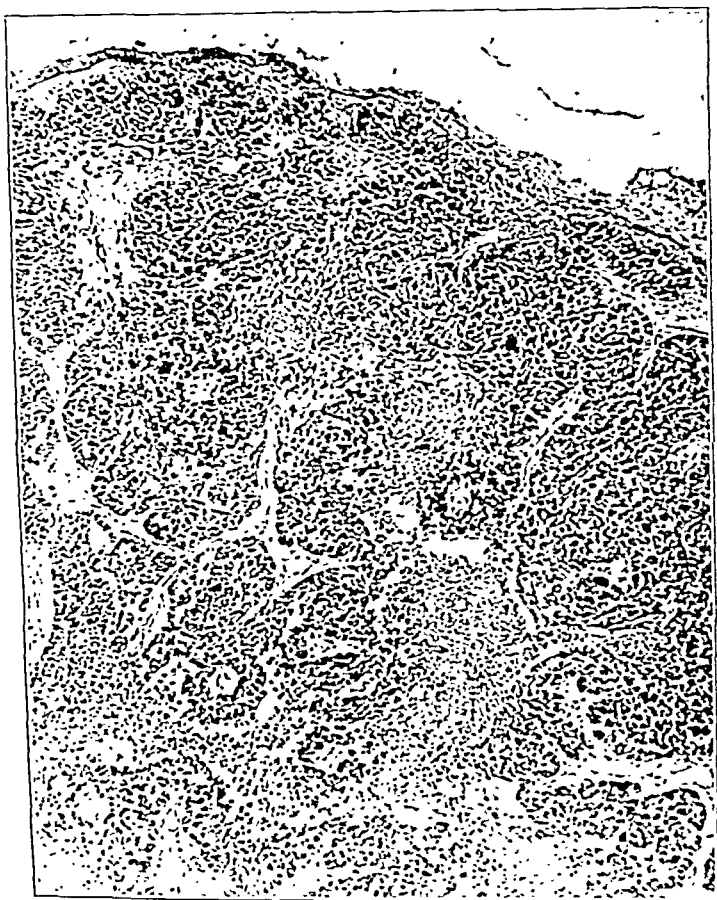


Fig. 1 (mouse 2, table 6).—Section of primary tumor. The animal received nothing aside from the routine diet. The lighter areas represent necrotic tissue, while the darker ones depict viable tumor. The relatively few black points denote pyknotic tumor nuclei and leukocytes. No evidence of calcification is seen. von Kossa stain;  $\times 75$ .

calcium, and that necrobiosis was not necessarily the result of the heightened calcific processes.

Table 2 reveals that the sesame oil per se had no effect on the deposition of calcium in either the neoplasm or the organs.





Fig. 2 (mouse 9, table 5).—Section of primary tumor. (Figures 2, 3, 4 and 5 represent the same mouse.) This animal received injections of viosterol. The black areas portray marked calcification of portions of the tumor. von Kossa stain;  $\times 75$ .

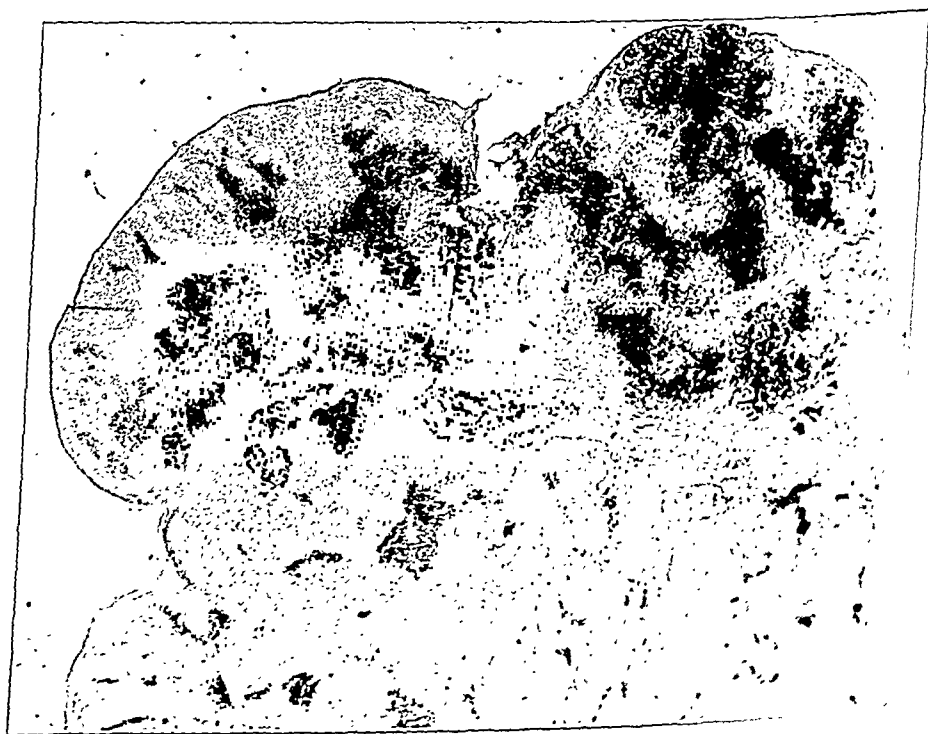


Fig. 3 (mouse 9, table 5).—Section of primary tumor. The black patches illustrate the general distribution of the calcium deposits. von Kossa stain;  $\times 75$ .

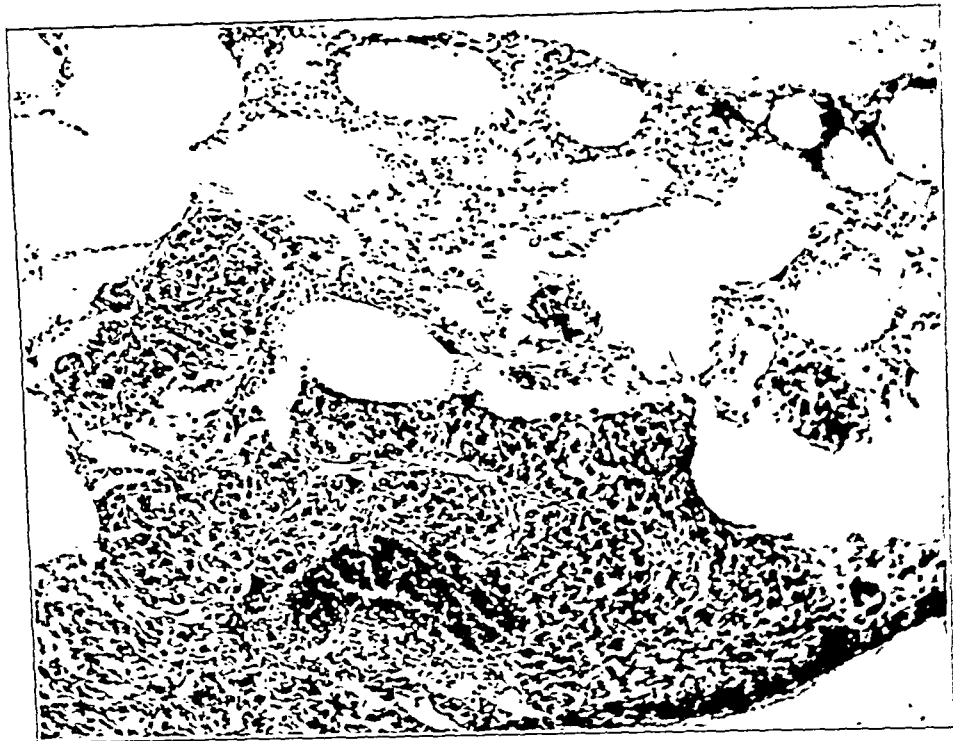


Fig. 4 (mouse 9, table 5).—Section of pulmonary metastasis. The black area of the central portion of the tumor represents marked calcification in contrast to none in the periphery or in the adjacent lung. von Kossa stain;  $\times 125$ .



Fig. 5 (mouse 9, table 5).—Section of lung. The calcium deposits correspond to the blackest areas. Depicted in the lower right hand portion of the photograph is an artery with partial calcification of the wall. The same pathologic process is in the bronchus (middle of figure) and to a lesser extent in the alveolar septums. von Kossa stain;  $\times 75$ .

Histologic studies showed that the presence of large amounts of calcium in the neoplasm did not apparently increase the mortality of the cancer cells or accelerate fibroplasia.

TABLE 7.—Experiment 2; Data on Viosterol Group, Tumor-Free Mice (Controls)

Mouse	Total Day*	No. of Doses	Microscopic Amount of Calcium			
			Lung	Stomach	Kidney	Aorta
1.....	15	5	None	None	None	None
2.....	43	14	Marked	Marked	Marked	Marked
3.....	48	17	Marked	Marked	Marked	Marked
4.....	48	17	Marked	Marked	Marked	Marked
5.....	48	17	Marked	Marked	Marked	Marked
6.....	46	16	Marked	Marked	Marked	Marked
7.....	48	16	Marked	Marked	Marked	Marked
8.....	48	17	Marked	Marked	Marked	Marked
9.....	48	17	Marked	Marked	Marked	Marked

\* Total days from the time of the first injection of viosterol to death.  
 Mouse 1 died too early to show characteristic changes of hypervitaminosis D.  
 There were nine tumor-free mice. Eight had calcification of the lung, stomach, kidney and aorta.

TABLE 8.—Experiment 2; Dosage

No. of Doses	Amount Each Dose,* Cc.	Total Dosage, Cc.	Period of Dosage, Days	Condition of the Mice
2,000 CLO				
1.....	0.064	0.064	1	Normal
2.....	0.048	0.112	4	Normal
3.....	0.064	0.176	8	Normal
4.....	0.048	0.224	11	Normal
5.....	0.064	0.288	15	Normal
6.....	0.064	0.352	18	Normal
7.....	0.096	0.448	22	Normal
8.....	0.096	0.544	25	Normal
9.....	0.128	0.672	29	Normal
10.....	0.160	0.832	32	Normal
10,000 CLO				
11.....	0.016	0.016	34	} Anorexia, loss of weight, bloody diarrhea
12.....	0.064	0.080	36	
13.....	0.096	0.176	38	} Tendency to inactivity, ruffling of hair
14.....	0.096	0.272	40	
15.....	0.096	0.368	42	
16.....	0.096	0.464	44	} Some mice have died; others are unsteady, and tails are cyanotic
17.....	0.128	0.592	46	
18.....	0.128	0.720	48	
19.....	0.128	0.848	50	

\* In terms of a sesame oil solution of irradiated ergosterol having a biologically-assayed antirachitic potency of 2,000 CLO in the first sample and 10,000 CLO in the second.

The deposition of calcium in the tumor may have slightly preceded that in the organs, but in the latter stages of the disease the process was apparently as marked in one as in the other.

The observations made on the tumor-free mice (table 7) show that the calcification of the animal tissues was independent of the presence of the carcinoma, and in addition confirms the work of previous investigators.

In our animals the natural course of the Twort carcinoma did not seem to be influenced significantly by the giving of large amounts of viosterol. There may have been more early regressions, but tumors which did progress advanced at the usual rate and were able to metastasize to the customary site, i. e., the lungs.

After approximately thirty-four days the toxic effects of the activated ergosterol were manifested in obvious derangements in the general condition of the animals (table 8). Since the signs of illness appeared simultaneously with the administration of the more potent solution (10,000 CLO), and since furthermore the first dose was more than proportionately reduced in quantity, the occurrence of these signs at that particular time was considered but a coincidence.

#### COMMENT

The calcification of an experimental tumor by means of viosterol might well raise the question as to its clinical application. The same problem has presented itself in the therapy of tuberculosis. In the first part of this paper it was pointed out that T. D. Spies had experimentally produced calcification of tubercles by giving large amounts of irradiated ergosterol. He warned against the clinical use of proportionate dosages in people and would therefore make no presumption that his work could, or should, be duplicated in patients. Becker<sup>26</sup> and others have reported good results in persons suffering from phthisis, but on the whole the evidence has not been convincing.

From our observations we should surmise that in human carcinomas the results of giving large doses of viosterol would be disappointing. This is based on the facts that the fully established tumors in our animals were not restrained, and that the necrosis seemed no greater than in the control neoplasms. Moreover, as medication continued, the animals became ill and died. It might be desirable to test the effects of therapeutic dosages of viosterol in mice bearing various types of tumors, but a sufficient period of time should elapse so that a possible connective tissue reaction might be instituted, and care should be taken in order that the natural resistance of the host to the neoplasm would not be lessened through damaging the viscera with toxic doses of activated ergosterol.

Since both lead and calcium have an affinity for osseous tissue, it is interesting to conjecture the results that might be obtained from such therapy directed toward bone tumors. Certain interchanges which occur

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26. Becker, O.: Vigantol-Kalkbehandlung bei Lungentuberkulose, Deutsche med. Wchnschr. 56:1007 (June 13) 1930.

in vivo between lead and calcium indicate the possibility of viosterol being able to influence the deposition of lead.

The increased density due to calcium deposits might theoretically offer a possible aid to roentgen diagnosis, but in order to be safe, and therefore of clinical value, the calcification of the tumor should precede that of other tissues. At present such a selectivity does not seem probable. Since neither the cancer nor the tissues had any apparent influence on the calcific processes in the other, one would assume that the deposition of calcium was a general phenomenon and that there was no greater susceptibility of the neoplasm than of the stomach, lungs, aorta and kidneys.

TABLE 9.—*Summary of Data*

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Experiment 1:

Viosterol group: 8 mice with tumors; all revealed calcification of the tumors (table 1)  
 Sesame oil control group: 5 mice with tumors; none revealed calcification (table 2)  
 Control group, receiving only usual diet: 6 mice with tumors; none revealed calcification (table 3)

Experiment 2:

Viosterol group: 13 mice with tumors; all revealed calcification of the tumors (table 5)  
 Control group, receiving only usual diet: 8 mice with tumors; two revealed very slight calcification of the tumors (table 6)  
 Control group, without tumors but receiving viosterol: 9 mice without tumors; eight revealed calcification of certain organs (table 7)

Combined data of experiments 1 and 2:

Viosterol groups: 21 mice with tumors; all revealed calcification of the tumors  
 Control groups; receiving only usual diet: 14 mice with tumors; two revealed very slight calcification of the tumors  
 Control group, receiving sesame oil containing no viosterol: 5 mice with tumors; none revealed calcification  
 Control group, receiving viosterol but bearing no tumors: 9 mice without tumors; eight revealed calcification of certain organs

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One criticism that might be offered against the present studies is that the animals receiving injections of viosterol were not rigidly separated from the others. Nelson and Steenbock<sup>27</sup> have shown that the feces of rats contain protective amounts of vitamin D after the animals have been subjected to the ultraviolet rays. It is possible that coprophagy might have enabled some mice that did not receive injections to secure a quantity of vitamin D from their cage mates that had received viosterol by way of the peritoneal cavity and thus explain the slight calcification of tumors in two mice which were given nothing but the diet. However, one does not know that the results of Nelson and Steenbock would be obtained under our experimental conditions, and, moreover, the marked uniformity of our findings was preclusive of any serious investigative errors.

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27. Nelson, E. M., and Steenbock, H.: Fat Soluble Vitamins: Further Observations on Antirachitic Action of Irradiated Animals on Non-Irradiated When Placed in the Same Cage, *Am. J. Physiol.* **73**:341, 1925.

## SUMMARY

We have endeavored to rationalize the present study on the basis of clinical and experimental observations which have shown that in a general way the presence of a large amount of calcium in an epithelial tumor is indicative of growth retardation.

Because dependable researches have proved that certain organs of the body may be overloaded with calcium due to the influence of irradiated ergosterol, it was thought that calcium might be deposited in a carcinoma as a result of the host receiving large amounts of viosterol. A more direct lead was that given by T. D. Spies, who clearly demonstrated that such an effect could be produced in tubercles.

The materials and experimental methods employed have been described in detail, and the results obtained have been portrayed in tables and photographs. The summary of the data may be found in table 9.

The chief point of interest was that an intense calcification of portions of a mouse carcinoma was obtained by means of viosterol.

A discussion of the effects secured has been appended. This includes a criticism of the present investigation and its application to the clinic.

## CONCLUSIONS

1. Toxic doses of viosterol produced calcification in actively growing mouse carcinomas and their metastases.
2. The heightened calcific process in the neoplasm was apparently concomitant with that in certain viscera.
3. Except in the early stages of therapeusis and tumor growth, the biologic behavior of the host seemed more affected than that of the neoplasm.

# A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 426)

## BLADDER

*Carcinoma.*—Barringer<sup>31</sup> stated that the technic of the suprapubic method of implantation of radon seeds into vesical tumors as developed at the Memorial Hospital is comparatively simple. It has an operative mortality of between 3 and 4 per cent, yet is successful in controlling many tumors that are inoperable. It is especially successful in dealing with tumors of the base of the bladder and trigone.

In some cases the implantation is not properly performed. There are two principal reasons for this: (1) The surgeon who is responsible for the diagnosis and the operation is usually not trained to give treatment with radium, and (2) an adequate number of radon seeds of a proper strength is often not available. For suprapubic implantation one should have at hand half again as many radon seeds as one thinks may be required, since neither cystoscopy nor a cystogram can possibly indicate the extent of a large vesical tumor.

In a specific consideration of the control of vesical carcinoma by radium, there are two methods of approach: radium applied through the open bladder and through the cystoscope. Each of these methods has been successful in a comparatively large series of cases. The supra-

31. Barringer, B. S.: The Technique of the Suprapubic Implantation of Radium Seed into Bladder Carcinoma. *Surg., Gynec. & Obst.* 55:487 (Oct.) 1932

pubic method of approach is the one of choice. Points in favor of always using it are: the ease with which it can be done, and the relatively low mortality. In the first 109 consecutive cases treated suprapubically by Barringer, he stated that 4 patients died in the hospital, an operative mortality of 3.6 per cent. Since that time the operative mortality in his cases has risen to about 4 per cent. This percentage is low when one considers that many inoperable cases are included.

During the last six years, Barringer stated, spinal anesthesia has been used in the Memorial Hospital. In none of the cases, now numbering more than 1,000, has death resulted from anesthesia. The shock to the patients has been minimized, and they are able to take fluids in much larger quantities, and sooner, than after general anesthesia.

If the tumor is papillary, the papillary portions are removed by some form of cautery, so as to expose the base of the lesion. If the tumor is flat and the surface sloughs and ulcerates, light cauterization should be done to help control the infection. Radon seeds, of a strength between 1 and  $1\frac{1}{2}$  millicuries, should then be implanted at the base of the tumor. To treat a large tumor accurately at least twenty radium-bearing needles should be used. A line of these needles is placed on the extreme edge of the tumor, then a second line above this.

The patient does not experience any reaction from the radium until from ten days to two weeks have elapsed, and the height of the reaction occurs perhaps a month after implantation and then slowly recedes. Pain and urinary frequency result. The larger the dose of radium and the nearer the tumor is to the vesical neck, the greater is the reaction. In making the implantation one does not pay any attention to the ureteral orifices, even if the tumor is directly over one or both.

Boyd<sup>32</sup> called attention to the significance and frequency of urinary obstruction in carcinoma of the bladder, which can, in some cases, be satisfactorily treated and prevented by nephrostomy. Nephrostomy should be used to prepare patients, particularly for cystectomy, when it is a more rational procedure than ureteral transplantation to the bowel, at least until ureteral transplantation by the Coffey technic is proved to supply adequate drainage as long as it is needed. Boyd stated that the literature on carcinoma of the bladder seems to indicate that urologists do not generally appreciate the frequency with which urinary obstruction occurs with vesical growths, nor do they often enough take advantage of the opportunity that is offered by nephrostomy to cure or relieve the suffering of patients with carcinoma of the bladder.

In the past, two essential factors have been lacking to make nephrostomy as popular an operation as it should: (1) satisfactory tubes and

32. Boyd, M. L.: Indications for Nephrostomy and Nephrectomy in Carcinoma of the Bladder, *J. A. M. A.* 99:1226 (Oct. 8) 1932.



containers for urine, and (2) an operative technic which avoided hemorrhage and leakage of urine about the tube. An efficient method of urinary drainage and an efficient apparatus are illustrated by a case in which nephrostomy had been performed and eight years later the patient was in good health, had married and was carrying on the business of life satisfactorily.

Hirsch and Schmidt<sup>33</sup> stated that the diffuse infiltrating type of carcinoma of the urinary bladder, according to the experience of urologists, has an insidious clinical course. The usual symptoms may be absent, especially hematuria. The outstanding anatomic features are the marked infiltration and thickening of the vesical wall and the absence of a conspicuous tumor of the lining epithelium.

In one case, the cells of the tumor were small, and in regions in which compression, necrosis and deep penetration of the vesical wall had not masked the structure, the arrangement was papillary. This papillary form aligns the infiltrative carcinomas of the urinary bladder with other papillary tumors of the urinary tract. If this papillary arrangement is not recognized in the examination by the pathologist, the small size of the carcinomatous cells and their diffuse infiltration of the wall of the bladder may lead to the histologic diagnosis of round cell sarcoma or lymphosarcoma.

Winsbury-White<sup>34</sup> reported a case of leukoplakia of the bladder. The initial symptom was hematuria, associated later with increased frequency, urgency and difficulty of urination, of twenty-seven years' duration. Cystoscopy was unsatisfactory because the mucosa of the bladder was irritable and there was a large ulcer on the trigone. The bladder was drained suprapubically, and after twelve weeks, when the sinus had not closed, four 1.3 mg. radium needles were implanted in the ulcerated area.

After nine months, the symptoms were as severe as before operation. Cystoscopy was again impossible because the bladder was highly irritable. Study of the upper and lower parts of the urinary tract disclosed no etiologic factor. Urograms made after intravenous injections gave essentially negative results. Moderate infection was present, and colon bacilli were found on culture. The Wassermann reaction gave negative results. Microscopic sections from the vesical wall revealed the characteristic changes of leukoplakia. The epithelium was squamous, with keratinization of the superficial layers, a well marked stratum granulosum and well developed tongues of epithelium projecting deeply into the underlying connective tissue. The outstanding feature was the

33. Hirsch, E. F., and Schmidt, L. E.: The Diffusely infiltrative Carcinoma of the Urinary Bladder, *Am. J. Cancer* **16**:882 (July) 1932.

34. Winsbury-White, H. P.: Leucoplakia in the Urinary Tract, with a Report of a Case, *Brit. J. Surg.* **20**:49 (July) 1932.

uniform distribution of the change over the whole of the vesical mucosa except that the trigone was ulcerated.

In considering the etiology of leukoplakia Winsbury-White called attention to the accumulated evidence that it is a deficiency disease. It has been demonstrated that epithelial metaplasia not confined to but including the urinary tract is common if the diet is deficient in vitamin A. Although infection is commonly associated with leukoplakia, it cannot be assigned as a cause.

*Bilharziasis.*—Makar<sup>35</sup> described the cystoscopic appearance of bilharziasis of the bladder. The changes are the result of infiltration of the wall with ova of Bilharzia. The infiltrations may be superficial, producing pathologic changes, but the cystoscopic picture is typical, although at times it is confused with that of carcinoma or tuberculosis. The process may be deep, leaving a normal mucosa. More commonly, however, the deep lesions produce changes in the mucosa.

The lesions may be divided into those of the mucous membrane, the submucosa, the deep vesical tissues, the intravesical portion of the ureters and the complicating lesion. The characteristic lesion is the bilharzic tubercle, which is not unlike the tubercle of tuberculosis. At times the tubercles coalesce to form the bilharzic nodules, which in turn may group to form the bilharzic node. The nodules may form ulcers, which in cases without infection are small, superficial and devoid of slough. With the advent of infection, secondary changes in the ulcers take place.

Bilharzic papillomas commonly occur on the posterior wall and at the ureteral orifices. Calcification is common in these lesions, and roentgenograms are characteristic. Infiltration of the deep vesical tissue with bilharzic ova and the accompanying fibrosis and calcification produce submucous masses with ulceration, pedunculation and, later, marked contraction of the bladder. The bladder infested with Bilharzia may become severely infected. One of the most common and distressing complications is bilharzic carcinoma, which has been named "irritation cancer," because its origin is attributed to prolonged irritation by myriads of bilharzic ova.

*Diverticulum.*—Martin<sup>36</sup> stated that unrecognized diverticula of the bladder encountered during the course of prostatectomy are a source of great trouble; an attempt should always be made to diagnose and treat them before operation. Although the diagnosis is most often made in cases of infection or in difficult cases in which numerous cystoscopic

35. Makar, Naguib: Cystoscopic Appearance of Bilharziosis of the Bladder, Brit. J. Urol. 4:209 (Sept.) 1932.

36. Martin, L.: A propos du traitement des diverticules de la vessie au cours de la prostatectomie, J. d'urolog. 33:182 (Feb.) 1932.

examinations are required, one is occasionally confronted with a case of acute retention in which the urine is clear; this does not suggest a diverticulum. When the diverticulum is not too large, adequate drainage may be secured by simple débridement, followed by packing with gauze, without recourse to grave operations which are designed to remove the diverticulum. It is advisable to suture together the two mucous membranes to avoid diffusion of infection in the cellular tissue if this has passed beyond the vesical wall.

If diverticula are large, however, palliative treatment will fail. In individual cases operative methods include multiple scarification, removal of the spur on one side of the neck of the bladder between two clamps, followed by débridement with scissors or knife; simple incision and tamponade may also be used. All these ameliorate the condition, and if any one of them is successful in suppressing the urethral or prostatic obstacle or sclerosis of the neck of the bladder, satisfactory results may be obtained.

[COMPILERS' NOTE.—In the majority of cases in which prostatectomy is performed or in which residual urine is present, cystoscopy should be accurately performed and a cystogram should be taken in an effort to establish a proper diagnosis before operation. When the diverticulum is not of the retentive type, simple removal of the obstruction from the vesical orifice by prostatectomy or resection of the vesical neck by the electrosurgical method or by the punch operation will be sufficient to relieve the condition. Lowsley and Gutierrez<sup>37</sup> have described the three-stage method of treatment, to be used when the diverticulum is of the retentive type: first stage, suprapubic drainage, to relieve infection and secure gradual renal decompression; second stage, perineal prostatectomy, when the hypertrophy of the adenomatous prostate gland interferes with the normal drainage of the bladder, and third stage, suprapubic or transvesical diverticulectomy to remove the sac of the diverticulum. Concomitant associated changes, such as tumors or calculi, have repeatedly been reported in the literature. Hence it is obvious that when a diverticulum is of the retentive type it must always be removed in toto in order to obtain permanent cure.]

*Umbilical Fistula.*—Duclaux and Blondin<sup>38</sup> have assembled from the literature 35 cases of uracho-umbilical, or as Begg prefers to call it, vesico-umbilical, fistula. They reject, or accept with reserve, 30 of the 56 cases reviewed by J. Monod previous to that date. They accept a

37. Lowsley, O. S., and Gutierrez, Robert: *Operative Intervention for the relief of Diverticulum of the Urinary Bladder: Analysis of Fifty-Four Cases*, J. Urol. **19**:459 (April) 1928.

38. Duclaux, Henri, and Blondin, Sylvain: *L'ouraque et les fistules urinaires de l'ombilic*, Rev. de chir., Paris **71**:45 (Jan.) 1932.

total of 86 cases that are indisputable, to which they have added 1 case of their own. Of these 87 patients 51 were males, and 60 were newly born infants or were observed during the first weeks of life. It is not exceptional, however, to see such a fistula appear in adults or in aged persons. In some of these cases there had been an umbilical fistula in childhood, which had been closed, either by operative measures or spontaneously, and which in later years had reopened.

Certain predisposing causes were found: Thus, phimosis had occurred in 5 cases; atresia of the meatus, more or less complete, in 3; obliteration of the vesical neck in 1 case, and persistence of the omphalomesenteric duct in 1. In some cases there was a leaking umbilical granuloma or the opening of a small abscess at the level of the cicatrix.

As a rule, the members of the family ask for surgical treatment for what is recognized as a painful infirmity in the child. The prognosis depends on the extent of the malformations and often on the degree of resistance of the newly born infant. Infection of the upper part of the urinary tract has in a number of cases proved fatal. Three patients who died were between the ages of 25 and 28 years. Adenocarcinoma has been known to develop at the site of the fistula.

In favorable cases the fistula is easily obliterated; it may close spontaneously or following suitable treatment. When the discharge is free, it is easy to close the orifice, but as the tissues are fragile, it easily reopens. If the urine exudes drop by drop, owing to failure of the ventral cloaca to close, surgical closure is final.

Thirty-five cases of umbilical tumors were recorded. In 1 case there were two penes, and urination from them was simultaneous. Certain vesical conditions, such as calculi, were observed in some cases. Begg has pointed out a tendency toward lobulation of the kidneys, or to kinks or dilatation of the ureters. Abscess and cystitis were present in 5 cases, tuberculous lesions in 3 and carcinoma in 3.

Diagnosis is usually easy. If the child is newly born, cicatrization is slow after fall of the cord; the integument is irritated by the liquid flowing from the navel in greater or smaller amounts; actual inflammatory lesions may appear, or some form of torpid pruriginous dermatitis.

The umbilical region is in a state of tumefaction, with a veritable hernia protruding when the child cries. At one point of this protrusion, usually the lower part, liquid is seen flowing out through a fine orifice. The opening is sometimes masked by crusts, or if there is no tumor, hidden in a fold of the umbilical depression. The fluid may flow, spurt or be elicited by cries or pressure. It is always important to examine the lower passages carefully for phimosis. As a rule most of the urine flows out through the urethra; the umbilical discharges are less abundant, and exhibit a certain rhythm; thus in some cases the discharge may follow this course with the patient recumbent; in other cases either

route may be used at will, or the fistula may be used only at night, etc. In the author's case, the diagnosis was made on the basis of the appearance of pyuria observed a few days after the umbilical discharge began, thus seeming to prove a connection with the bladder. Delore stated that infection passes from the umbilicus to the bladder; Legueu stated the reverse.

Various therapeutic measures have been tried. All have two ends in view: (1) to reestablish complete permeability of the lower part of the urinary passages, and (2) to attempt to obliterate the fistulous umbilical orifice. For the first, circumcision should be performed if there is phimosis. For the second there are various surgical procedures. Compression of the orifice was successful in only 1 case recorded. Superficial or intracanalicular cauterization with caustics or the actual cautery has given good results. Ligature of the umbilical tumor has been successful in some cases and has failed in others. Suture after freshening of the canalicular surfaces has been tried, but may lead to hernia. The urachus may be opened, the mucosa destroyed with a curet, the lower extremity tied at a proper distance from the bladder, the wall sutured into its upper half and the lower half plugged with a tampon. Or again, the peritoneum may be opened, and the urachus isolated and resected, with proper protection of the greater cavity; the lower extremity may be ligated, and the wall completely closed, with care to fix the stump well outside of the peritoneum to avoid the risk of intraperitoneal fistula. Monod performed total resection of the fistulous urachus, after opening the peritoneal cavity; he closed the vesical breach in three layers, with solid recomposition of the abdominal wall, and obtained an excellent result. Pauchet performed complete resection of the fistula without opening the peritoneum, a difficult procedure.

At present there seems to be agreement that the urachus should be completely extirpated, if possible, without opening the peritoneum, but usually the procedure is intraperitoneal, with protective technic. A wise precaution is to close the umbilical orifice before opening the abdomen, by means of a purse-string suture. The vesical suture is done according to the customary rules. A catheter is left in place for from three to five days.

The indications for this operation are wide, and one should not hesitate to apply it in the case of older children and adults. The only contraindications are youthfulness and poor general condition of the patient or the presence of a high degree of infection. In newly born infants, spontaneous closure is not unusual. On the other hand, in the first week of life surgical procedures of any kind seem to present a certain risk; the indications at this time are for minor measures, such as cauterization and disinfection of the fistulous tract with frequent aseptic dressings. If the orifice closes, it may not present any true solidarity.

and should be watched for possible reopening, in which case an operation, perhaps total resection, may be done at a later period.

#### PROSTATE GLAND

*Transurethral Resection.*—Boyd and Bailey<sup>39</sup> stated that in order to discover what tissues are removed at transurethral resection of large, benign prostatic growths, and also what reaction takes place in the tissues about the resected area, they have studied the anatomy of benign prostatic hypertrophy. In 4 cases in which the prostate glands were large, they performed transurethral resection, and then after one, two and four weeks they performed a suprapubic prostatectomy. In all of the cases the bladders were infected, and in 3 of them preliminary suprapubic drainage had been instituted.

The authors stated that observation of these cases led them to believe that in transurethral resection for benign hypertrophy of the prostate gland, the vesical sphincter is cut or partly removed. Also the muscle fibers running to the prostatic urethra from the trigone are cut, and their assistance in the performance of voluntary urination is lost. In cases in which the bladder is infected there is a marked inflammatory reaction about the resected region, although suprapubic drainage has been established before the resection. The healing of the resected surface is usually slow, and the cut surface may not heal completely for three months.

Boyd and Bailey further stated that cutting the vesical sphincter probably accounts for at least part of the relief from urinary obstruction which is generally obtained by resection, in spite of the inflammatory reaction which occurs about the resected region and regardless of the loss of the assistance which the pull of the trigonal muscle on the vesical sphincter offers in voluntary urination. They stated that the important factor is the knowledge of cutting the sphincter in performing transurethral resections, and this knowledge will lead to general improvement in the results obtained by the operation and will prevent the poor results which occur when insufficient tissue is removed.

Thompson<sup>40</sup> stated that the development of transurethral resection has greatly reduced the risk of surgical treatment in cases of prostatic obstruction. This has been a great benefit to many men suffering with enlargement of the prostate gland, particularly to those who are more than 70 years of age, and to those of all ages who are in poor general condition.

39. Boyd, M. L., and Bailey, M. K.: Transurethral Prostatic Resection in Benign Prostatic Hypertrophy, *Piedmont Hospital Bulletin*, September, 1932, vol. 6, no. 1.

40. Thompson, G. J.: Transurethral Prostatic Resection for Patients in Poor General Condition, *Proc. Staff Meet., Mayo Clin.* 7:513 (Sept. 7) 1932.

In the last year it has been found possible to remove the prostatic obstruction of aged and handicapped patients by transurethral operation. Many of the patients who were wearing suprapubic tubes were recalled, and vesical function was restored. Also, men who have required catheterization several times daily over periods of two years or more have been entirely relieved by an operation which in most cases requires only four days in the hospital. The social and economic aspects of such complete relief are evident. Patients who have gone into seclusion have become interested again in human associations and have returned to normal ways of living. In some cases they have been able to resume their former occupations.

The transurethral operation, properly performed, carries so little risk that in the Mayo Clinic the surgeons feel justified in performing it in all cases except those in which patients are bedridden or in which the value of urea is more than 100 mg. for each 100 cc. of blood.

In order to have available evidence of the relative safety of the transurethral operation, 25 cases in which it was performed on patients who were more than 70 years of age have been reviewed and compared to 25 cases in which patients of similar age were submitted to prostatectomy. There were no deaths among patients who underwent the transurethral operation, whereas 4 of those who underwent prostatectomy died. Many of the patients in the former group were refused a major operation, and those on whom prostatectomy was performed had apparently a good chance for recovery; therefore, it is clear that the patients who constituted the poorest risks were cared for by transurethral operation.

Transurethral operation has greatly reduced the hospital expense for patients. This is particularly noticeable in cases in which preliminary suprapubic drainage is unnecessary; in such cases the average postoperative time in the hospital is only nine and six-tenths days as compared with the average of thirty-two and one-tenth days in cases in which prostatectomy is performed in one stage. Special nursing care is usually required after prostatectomy and rarely after transurethral resection.

Saving time and money is of less importance than saving postoperative strain and discomfort. Many patients are operated on under spinal anesthesia induced by 50 mg. of procaine hydrochloride. Few patients miss more than one meal after the operation; most of them are up and have to be cautioned not to walk too much the day following the operation instead of barely being able to sit up in a chair. The last death occurred nine months ago, following which 210 patients have been operated on, and it has not been necessary for any of them to have subsequent prostatectomy.

Many men suffering from the discomfort of suprapubic drainage or leading a "catheter life" could be relieved by this operation, and they should be made aware of the fact.

Bumpus <sup>41</sup> stated that the late results of transurethral resection would indicate that recurrence of the obstruction even in cases of adenofibromatous hypertrophy is the exception, for in only 3 of 75 such cases was prostatectomy necessary later; in 2 of these it was performed so soon after resection as to exclude the possibility of recurrence, indicating that the faulty results were due to failure to remove sufficient tissue. He expressed the belief that adequate removal of all obstructing tissue not only is essential to complete elimination of residual urine but is the best insurance of a satisfactory postoperative course, for a raw surface at the vesical neck, in the presence of residual urine, is a potential source of secondary infection. Hence, every effort should be made to insure complete emptying of the bladder immediately after resection. Bumpus excises the tissue with a tubular knife, used through a modified Braasch cystoscope, and controls the bleeding by electrocoagulation of the incision both before and after each incision. By this means destruction of tissue is kept at a minimum, and healing of these incised areas seems to be more rapid than when the tissue is removed by a loop electrode. There is the added advantage that any postoperative bleeding usually will occur early in convalescence, and will not take place at some more distant date, when sloughs from too extensive coagulation come away.

Bugbee <sup>42</sup> stated that with a clearer understanding of the pathologic changes of prostatic obstruction and its far-reaching effect on the various systems of the body, with the institution of careful study of the various bodily functions, especially renal function, with the proper preparation of the patient for operation and with the well conceived operative technic and postoperative care, prostatectomy for hypertrophy has taken a place where it compares favorably with any major operation on any similar class of patients who are operative risks.

The author further explained that with the perfection of the modern cystoscope and urethroscope and the use of electrodes capable of carrying high frequency currents of high potentiality, resection of the prostate gland, namely, the removal of sections of tissue of sufficient size to relieve obstruction, is possible in carefully selected cases, under sight and with the control of hemorrhage.

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41. Bumpus, H. C., Jr.: Results of Prostatic Resection Over a Period of Seven Years, *J. A. M. A.* **99**:1836 (Nov. 26) 1932.

42. Bugbee, H. G.: Operative Relief of Prostatic Obstruction, *J. A. M. A.* **99**: 1832 (Nov. 26) 1932.



Randall<sup>43</sup> stated that there are only three major pathologic entities involving the prostate gland that cause vesical retention and that depend on operation for their relief or cure. These are carcinoma, median bars and glandular hypertrophy.

Knowledge of the pathology of prostatic carcinoma has advanced little in the last decade. Microscopically, the majority of these growths are true adenocarcinomas, and one startling feature is the early age at which some of them are found. For many years carcinoma of the prostate gland was thought to have its origin primarily in the posterior lobe, but today it is recognized that it may start in, and involve, any portion of the gland. Operation does not seem to effect a cure in malignancy of the prostate gland in enough cases to heighten enthusiasm. Obstruction in these cases is probably due to phlegmonous induration of all structures about the vesical outlet, with hampering of the sphincter and trigonal muscles and the recognized narrowing of the posterior part of the urethra. Relief of these changes by resection should be considered an advantage when accomplished, and palliative to the symptoms usually present.

Median bars are sites of fibrosis, which by inevitable shrinkage cause stenosis of the vesical orifice and result in retention of urine and all the symptoms of prostatism. All evidence points to this fibrosis as the result of prostatic infection of long standing. Residual urine in these cases is caused by hampered function and at times by actual fibrosis of the trigonal muscle. Relief by operation is understandable, and the virtue of resection has been amply proved clinically.

Randall stated that microscopically, prostatic hypertrophy gives uniformly the picture of an adenoma which in its growth forms a false capsule by pressure from centralized proliferation, and this false capsule is the line of cleavage which makes enucleation possible. The common types of hypertrophy may be presented as follows:

First, simple hypertrophy of the bilateral lobes. Here two glandular masses are separately undergoing enlargement. They are separately encapsulated and no matter how large they grow, they do not show any tendency to dilate the sphincter or enter the vesical cavity. Cystoscopic resection would be least likely to succeed here.

Second, solitary commissural hypertrophy is found. Arising from the posterior commissural glandular tissue, it assumes increasing size and may reach surprising growth without other portions becoming hypertrophied. This is one of the two varieties of enlargement of the "middle lobe." Highly obstructive to the function of the trigonal muscle, its gradual glandular growth is accompanied by hypertrophy

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43. Randall, Alexander: *The Pathology of Bladder Neck Obstruction*, J. Urol. 28:509 (Nov.) 1932.

of this muscle, as nature's effort at compensation. These cases afford the so-called "bars due to muscle hypertrophy."

Third, the two previous combined types are found, and when commissural hypertrophy is present to cause sphincteric dilatation, the lateral lobes promptly find room above and characteristically herniate themselves through the sphincter and assume intravesical prominence.

Fourth, the subcervical gland of Albarran may be found as a solitary hypertrophic growth. It is the second variety of enlargement of the "middle lobe." Submucous in origin, its obstructive virtue enhanced by its strategic position, it exhibits the ideal form of mechanical blockage to emptying of the bladder.

Finally, growth of subcervical and lateral lobes in unison is seen. This also is accompanied by sphincteric dilatation and intravesical protrusion. Function of the detrusor muscle fails, and it is rendered incompetent from both lesions; if the growth is unlimited and gigantic, resection is doomed to failure.

Alcock<sup>44</sup> reported that transurethral prostatic resection offers excellent vision, the possibility of removing accurately an adequate amount of obstructing tissue and an adequate control of hemorrhage.

Alcock's report is based on 175 patients on whom transurethral resection has been performed. As this experience covers only ten months, it is obvious that nothing can be said about ultimate results. No serious effort in the way of follow-up study will be made until at least one year has elapsed since resection. The youngest patient was 53 years of age, and only 5 patients were less than 60. The oldest patient was 85 years of age, and 12 patients were more than 80. One hundred and three patients (58.8 per cent) were between 70 and 80 years of age, and 115 (65.6 per cent) were more than 70. The average age for the 175 patients was 71.4 years. Fifty-eight patients (33.3 per cent) had residual urine of 500 cc. or more. Only 3 patients had no residual urine, and only 7 had residual urine of less than 50 cc. Eighty-four (48 per cent) either had complete retention at the time of admission or gave a history of from one to several attacks. In 28 patients (16 per cent) carcinomas were present, and in 147 patients benign hypertrophy of different types was discovered. Six patients had had prostatectomy performed previously. Eighteen patients had had cystostomy. In several cases the cystostomy was performed by Alcock, previous to his taking up transurethral resection, and was done as a preliminary step to prostatectomy. In the other cases cystostomy had been performed elsewhere. Alcock has not done cystostomy as a preliminary step to transurethral resection for seven months.

44. Alcock, N. G.: Ten Months Experience with Transurethral Prostatic Resection, *J. Urol.* 28:545 (Nov.) 1932.

These patients were all prepared as though for prostatectomy. The anesthesia used was either transsacral or spinal block, the latter being used in a small percentage of cases; 200 transurethral resections were done on the 175 patients. Fifteen patients required 2 resections and 5 patients required 3. Fifteen of these 20 patients were among the first 50; of the remaining 5 patients, 3 had carcinoma.

A casual scrutiny of Alcock's charts that show the amount of tissue removed and the deaths as they occurred in chronologic order reveals the fact that the first 50 cases were the most troublesome. Results of the first 50 resections were somewhat discouraging. Only very small pieces of tissue were removed, and the total amount seemed to be entirely inadequate. Great difficulty was experienced and much time was consumed in controlling hemorrhage. The time required for these resections varied from one to two hours, or more. Practically all of the patients had postoperative reactions, and in more than 60 per cent of the cases the reactions were violent, as manifested by chills and a temperature from 101 to 104 F. that lasted from two to five days. Many of the patients were extremely sick. Twelve deaths occurred in the first 50 cases.

Alcock stated that the amount of tissue removed has little relation to the results attained, and practically no relation to the total size of the gland. The secret is not in determining how much tissue can be taken out, but rather in determining accurately exactly what the obstructing part is and then removing that part completely.

Alcock reported that the time consumed when operating in the first 50 cases was from one to two hours, or more. That has now been cut down; the resections at present are consuming from twenty-five to fifty minutes and it is seldom that the patient is on the table for more than an hour.

In Alcock's experience, hemorrhage was in no case a contributing cause to any of the deaths, and in no way affected recovery. In fact, he has not noted a hemorrhage that even caused an increase in pulse rate. He has not had to open a bladder to stop hemorrhage or been compelled to use any form of a bag or even a large catheter. He expressed the belief that the resectoscope offers a better chance of reaching the bleeding point and controlling it than any form of cystoscope. The secret of controlling hemorrhage is good vision, and good vision cannot be had if the hemorrhage is allowed to become too great before it is controlled. Alcock's rules are these: to continue to cut from one area until the hemorrhage begins slightly to interfere with vision; then to stop and carefully search for the bleeding points and to check the bleeding of each, one at a time. All bleeding from a particular area is controlled before another area is attacked. .

Bleeding during the first four or five days following operation has never been serious. In practically all of the cases there is at least a tinge of blood in the draining material, and in some cases considerably more than that. After leaving the hospital, several patients have had slight terminal hematuria about two weeks following resection.

Frequency during the first week or ten days after the catheter is taken out is the rule, and is to be expected. The frequency is often severe for the first five days; after that it decreases, but continues and should be expected to continue to some extent for three or four weeks. Alcock has not had a case of true incontinence. In many cases during the first week, the frequency is so great that it becomes uncontrollable. In practically all cases there is some residual urine during the first week or ten days after the catheter is taken out. This has varied from a few cubic centimeters to as much as several hundred cubic centimeters. In some of the first 50 or 60 cases Alcock made a second resection, but later he came to believe that this was not necessary, for he learned that residual urine will often decrease materially as the days go by.

Alcock stated that sepsis and uremia have been the complications most likely to be fatal. Gangrene of the bladder is a complication which should be kept in mind and guarded against by being careful not to cut too high in the direction of the bladder. Six cases of epididymitis occurred in 93 cases in which vasectomy was not done. Alcock intends to perform vasectomy on every patient as soon as the indwelling catheter is inserted in preparation for the resection.

Kirwin<sup>45</sup> reported on the use of his rotary resectoscope. The introduction of the new cutting and coagulating current of the McCarthy surgical unit enabled him to make use of a rotary wire electrode which simultaneously resects the tissues and seals the severed vessels. The electrode of his instrument works by a lever, its rotary motion definitely following the contour of the vesical neck, moving from right to left or left to right with equal facility. It leaves behind a smooth, cone-shaped orifice. Any bleeding point usually can be controlled by pressure on the sheath.

Other important features of Kirwin's instrument are: the fixed position of the rotary electrode while actual cutting is in progress (this prevents the loop riding over the tissue engaged in the fenestra instead of passing through it) and the small size of the sheath, which does not traumatize narrow urethras. Although the fenestra provides absolute protection for the vesical mucosa, so that the urologist need

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45. Kirwin, T. J.: The Evolution of Vesical Neck Resection: Past Results, Future Problems, and Use of the Author's Resectoscope, *J. Urol.* **28**:539 (Nov.) 1932.

not depend wholly on his skill to avoid piercing the wall of the bladder or urethra, the electrode reaches outside the fenestra in its eccentric swing, making larger resections possible; the fixation of the tissue to be resected permits every section to be brought out as it is cut off, keeping the field at all times unobstructed. With the instrument as it is now, Kirwin has had varying degrees of success and some failures. On the whole, the final results have been satisfactory.

Kirwin stated that the limitations of intra-urethral excision by cautery should be kept constantly in mind. The procedure will never entirely replace prostatectomy. An open operation will always be indicated for the patient in a good general condition who presents marked intra-urethral and intravesical protrusion of the lateral lobes and a hypertrophied middle lobe. When the transurethral route is followed, however, exactly the same preoperative precautions must be observed. The result is identical with that expected from perineal or suprapubic prostatectomy; therefore, the preliminary procedures should be the same.

Kirwin stated that 78 patients have now been operated on by this method, and 3 deaths have occurred, including 1 from cerebral hemorrhage which took place ten days after resection.

McCarthy<sup>46</sup> stated that at present the consensus in his department at the New York Post-Graduate Hospital is that endoscopic revision of an obstructing prostate gland should be limited to the correction of prostatic fibrosis, the so-called "collar condition," small and moderate-sized middle lobes and moderate-sized combined middle and lateral lobes.

Patients with infected prostate glands, even those included in the category before mentioned, who bleed readily on instrumental examination or who manifest pronounced fluctuations of temperature following such inspection should be carefully scrutinized. The enormous, the succulent or spongy prostate gland, the frankly enlarged, readily bleeding type and forms of encroachment such as angular conformation or infiltration that inhibit free movement of the instrument should be reserved for primary cystotomy and later revision or prostatectomy.

Up to the present decompression by catheter has been used in most of McCarthy's cases. The few cases in which suprapubic drainage was instituted were associated with vesical calculi. In all but the occasional case the method of decompression has been tolerated by the patient and satisfactory to McCarthy. For the most part the anesthetic used has chiefly been procaine hydrochloride, given by the caudal and paravertebral routes, and supplemented with urethral instillations of piperidinopropanedial diphenyl urethane (diothane). McCarthy feels that canalization

46. McCarthy, J. F.: A Technical Consideration of Endoscopic Revision of the Obstructing Prostate, *J. Urol.* **28**:519 (Nov.) 1932.

or tunneling of the urethra from the internal sphincter immediately posterior to the verumontanum, in other words an exaggeration of the normal tubular character of the deep urethra, should be sufficient.

After resection McCarthy advises using a number 24 French whistle-tip soft rubber catheter for drainage. The rule is to use the smallest possible soft rubber catheter for decompression and the largest possible whistle-tip catheter for postoperative drainage. Any interruption in drainage must be immediately corrected.

McCarthy's objective in the arrest of bleeding incidental to revision is that it is to be effected with a minimal amount of coagulation. To that end, perfect visualization is a necessary prerequisite. Thus, one can see a bleeding point and, however active it is, coagulate precisely at this point and not at the expense of the adjacent tissue. Not only to coagulate every bleeding point but to blanch every blush is his rule.

Cecil<sup>47</sup> presented a new electrical instrument for relieving obstructions at the vesical neck. The cutting system consists of a hinged bar that is permitted to penetrate the neck of the bladder after introduction of the instrument. Continuous irrigation is maintained, which permits visualization. The current is turned on by means of a foot switch. The bladder is filled with about 200 cc. of fluid. Then, with continuous irrigation, one observes the vesical neck through the cystoscope, causes the knife to project and passes the instrument backward and forward until it passes through freely.

Cecil has found this instrument useful in the treatment of hypertrophy of the prostate gland, of contracture at the vesical neck, of carcinoma of the prostate gland and of the various combinations of these conditions. Whether it is applicable to any given case must be determined by the operator after a thorough urologic examination.

*Carcinoma.*—Caulk and Boon-Itt<sup>48</sup> reviewed 222 cases of carcinoma of the prostate gland. They stated that chronic inflammation of this gland may be a predisposing cause. The cautery punch operation in conjunction with the use of radium and roentgen rays is their method of choice for relieving obstruction and for retarding the progress of the disease. In 72 per cent of the cases there was relief of obstruction. Twenty-nine per cent of the patients lived or are living more than three years, and 10 per cent more than five years after operation, which is a longer period than that afforded by prostatectomy.

The mortality from the operation, regardless of the fact that it was done in many cases on extremely ill patients, for whom prostatectomy

47. Cecil, A. B.: A New Instrument for the Endovesical Treatment of Prostatic Obstruction, *Urol. & Cutan. Rev.* **36**:194 (March) 1932.

48. Caulk, J. R., and Boon-Itt, S. B.: Carcinoma of the Prostate, *Am. J. Cancer* **16**:1024 (Sept.) 1932.

would not have been considered, is 2.5 per cent, whereas the mortality rate from prostatectomy in the authors' clinic is 17 per cent. With this treatment, it has not been necessary for patients to stay in the hospital as long as for prostatectomy.

Caulk and Boon-Itt further stated that the punch operation affords a definite means of accurately diagnosing carcinoma of the prostate gland in 80 per cent of all cases, early or late, which indicates that the disease, even in apparently early cases, is present throughout the substance of the gland.

Ferguson<sup>49</sup> reported that it is shown that carcinoma may and does arise in any portion of the prostate gland or its accessory lobules. Three clinical types of carcinoma of the prostate gland are described. Each type is characterized by its own clinical syndrome, pathologic features and prognosis. Pain, he stated, other than that due to urinary obstruction or metastasis to bone, is held to be pathognomonic of lymphatic extension, especially in the perineural lymphatic glands. He urged that the end-results of treatment should be evaluated on the basis of the clinical classification of the disease. He stressed the value of aspiration biopsy in the determination of radiosensitivity. He is of the belief that the selection of treatment is important, and that the effects of irradiation on the tissues of the tumor and adjacent structures should be considered.

#### TESTIS AND EPIDIDYMIS

*Tumors of Testis.*—McClure, Sanguinetti and Carlton<sup>50</sup> considered the radical operation and the interesting microscopic features in 2 cases of malignant disease of the testis. For many years the majority of testicular tumors were labeled sarcomas, and because of transmission of this type of tumor by the blood stream no consideration was given to an operation which would insure the removal of the lymphatic-bearing tissue. With the recognition of the carcinomatous nature of practically all malignant tumors of the testis, the problem was changed, and the principles were applied which govern the surgical treatment of carcinomas in other regions.

The first patient, aged 28, complained of a painless enlargement of the right testis of six weeks' duration. Following orchectomy a diagnosis of malignancy was made, and one month later the radical operation was performed, with resection of the region of lymphatic spread up

49. Ferguson, R. S.: Cancer of the Prostate: Study of Clinical Classification and of Effects of Treatment by Irradiation, *Am. J. Cancer* **16**:783 (July) 1932.

50. McClure, J.; Sanguinetti, H. H., and Carlton, C. H.: The Pathology, Diagnosis and Treatment of Two Cases of Malignant Disease of the Testicle, *Brit. J. Urol.* **4**:217 (Sept.) 1932.

to the renal vessels. The patient was alive and well twenty-one months after operation.

The second patient, aged 29, received an injury to the right testis three months before the radical operation had been performed for a malignant condition. No metastasis was demonstrable grossly, although what was taken to be a simple cyst of the cord at operation was shown to be a metastatic deposit in a lymph node. This patient died six months later; a large mass was found in the abdomen.

Microscopically, both of these tumors proved to be teratomas. However, in the second tumor the authors found, at the upper pole and distinctly separated from the tumor proper, which contained tridermic structures, a transition of the normal seminiferous tubules into the structure of a spermatocytoma or seminoma, separated by an imperfect, thin, fibrous capsule from the surrounding normal tissue. The transition from normal adult seminiferous tubules to malignant tissue was easily traced.

The authors apply these observations to a consideration of the divergent opinions as to the pathogenesis and classification of tumors of the testis.

[COMPILERS' NOTE.—Following the radical operation, the absence of demonstrable metastasis in the lymph-bearing area, carefully and completely removed up to the renal pedicle, is no guarantee against recurrence even after five years. A radical operation was performed for removal of an embryonal carcinoma of the testis (seminoma); careful and complete serial sections of the removed tissue did not disclose secondary invasion. A course of high voltage roentgen therapy was given, and the patient was alive and well seven years after the operation without demonstrable recurrences. However, the following year he died with a mass in the epigastrium which at necropsy proved to be metastasis in the preaortic nodes, at the level of the celiac axis. The region below the renal pedicle was free from metastasis and there was no local recurrence.

The radical operation is not so much a formidable procedure as it is inadequate, and it would seem that reliance will have to be placed on early diagnosis and orchectomy in the hope that secondary invasions have not occurred, or if they have, that they may be controlled by high voltage roentgen therapy.]

Ross<sup>51</sup> stated that 131 cases of tumor of the testis have been reported in which tissue morphologically identical with chorionepithelioma of the uterus has been found. These tumors are of further interest because in some cases they are associated with activity in the breast of the

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51. Ross, J. M.: Chorionepithelioma of the Testis, *J. Path. & Bact.* **35**:563 (July) 1932.



male, and recently cases have been reported in which the Aschheim-Zondek reaction has been positive.

Ross described a case in which pulmonary metastasis consisted of tissue morphologically identical with typical chorionepithelioma. The primary tumor was largely necrotic although small. The origin of syncytium and Langhans cells in the abdominal metastasis could be traced to small, cubical, darkly staining cells, which also gave rise to carcinomatous tissue and were found in blood vessels, lymphatic structures and the peripheral sinuses of lymph nodes. These cells gave rise to columnar epithelium and other structures in the cervical nodes. Ross concluded that the formation of chorionepithelioma of the testis is the expression of a process of specific partial differentiation of these pluripotential cells.

Peirson<sup>52</sup> stated that 46 cases of bilateral malignant tumors of the testis have been reported in the literature. Peirson has added another case. Treatment was by castration and prophylactic irradiation, and for three years and two months, which was up to the time of writing, the patient had remained free from metastasis. In this case castration produced few changes, with no loss of libido or potentia; this is often the case when the operation is performed on an adult.

*Tumor of Epididymis.*—Eisenberg, Simons and Wallerstein<sup>53</sup> reported a case of spheroidal cell carcinoma of the epididymis. It is the third case to be described. The tumor, grossly and microscopically, is identical with the neoplasm of the same name that appears in the testis. In using the term spheroidal cell carcinoma, the authors avoided the controversy as to the origin of this tumor implied in the terms seminoma and embryonal carcinoma. From their experience, they stated that the Aschheim-Zondek reaction is a valuable aid in the prognosis of spheroidal cell carcinoma of the testis and epididymis.

[COMPILERS' NOTE: It is of interest that the Aschheim-Zondek reaction is positive in some cases of tumor of the testis or epididymis. Recently this reaction was found positive in several cases of chorionepithelioma of the testis. On this basis, it was held that there was a physiologic equivalency of the two tumors, chorionepithelioma of the testis and of the uterus. Later, Aschheim found a positive reaction in a case of tumor of the testis in which a chorionepithelioma could not be found. Apparently this reaction is of more aid in suggesting malignancy than in indicating any specific type of growth.]

52. Peirson, E. L., Jr.: A Case of Bilateral Tumors of the Testicle, With Some Notes on the Effect of Castration of the Adult Male, *J. Urol.* **28**:353 (Sept.) 1932.

53. Eisenberg, A. A.; Simons, Irving, and Wallerstein, Harry: A Case of Spheroidal-Cell Carcinoma (Seminoma) of the Epididymis, *Am. J. Cancer* **16**:875 (July) 1932.

## URETHRA

*Infection.*—Salleras<sup>54</sup> reported a case of perivesical abscess following rupture of the posterior part of the urethra two years previous to observation. The patient had received a blow on the perineum, after which he had observed a few drops of blood issuing from the urinary meatus. Five hours later he could not urinate, and was catheterized. Three days later another attack of retention occurred, with a heavy chill followed by fever. Since then he had had no similar attacks, but he began to suffer with incontinence after six months, and observed that the urinary stream grew constantly smaller, until almost complete obstruction had developed. The hypogastric region was greatly increased in size, with a tumefaction reaching from the symphysis pubis to the umbilicus; the swelling was round, smooth and uniform, hard on palpation and dull on percussion. The urethra admitted only a filiform bougie, and catheterization caused scarcely any decrease in the size of the tumor. The cystogram revealed a typical "old man's bladder," although the patient was only 21 years of age. The opaque substance presented a festooned outline all around its perimeter, of irregular shape and with no contact with the bones of the pelvis or any sign of rupture or luxation of these. The senile appearance was caused by the presence of an abundance of cellules or diverticula and columns. The lateral oblique view also gave evidence of a goodly space separating the organ from the symphysis pubis.

The history of an old rupture, dysuria, urinary obstruction, incontinence and elevation of temperature pointed to a vesical phlegmon, but it was thought possible that the condition was a connective tissue tumor. On opening the abdomen by vertical and transverse incisions, with a view to exploring the bladder, an abscess was revealed that contained a large quantity of thick pus; it was of hard, woody consistence and occupied almost the entire pelvic cavity; this was drained.

Surgical intervention clarified the diagnosis: the urethrorrhagia demonstrated the rupture of the posterior urethra, for only thus could the perivesical hematoma be produced, since it is known that hematomas of the anterior urethra are periurethral. If it is assumed that rupture of the posterior urethra occurred, the perivesical hematoma following was the immediate consequence, and infection was shown by the chills, high temperature and retention three days later. The infected hematoma then became organized around the bladder. Traumatic stricture following the rupture explained the incontinence of urine on the basis of residual urine and overflow, a symptom that dominated the picture for

54. Salleras, J.: *Flemón leñoso perivesical, secundario a ruptura de uretra posterior*, Rev. de especialid. 6:1070 (Nov.) 1931.

eighteen months; at the end of this period, reactivation of the infectious process occurred, with fever, a rapid increase of the inflammatory perivesical tumor and a poor general condition. Operation made it possible to follow the distinct phases of the process up to the formation of the abscess, which was then discovered.

Liberson<sup>55</sup> stated that the painful heel noted in gonorrheal infection is due to both bony exostosis and the infiltration of soft tissue over it. Of 924 patients with infection admitted to the United States Marine Hospital during a period of four years, more than 3 per cent of these with complications had gonorrheal periostitis, with or without active infection in the genital tract.

Surgical treatment for gonorrheal exostosis is not entirely satisfactory on account of the prolonged preoperative and convalescent period and the frequency of recurrence. Local high voltage roentgen therapy, simultaneous with general measures to cure the gonorrheal infection when present, shortens the average stay in the hospital and produces a more permanent result in a larger number of cases.

#### UROGRAPHY

Moore<sup>56</sup> stated that pyeloscopy, in combination with serial pyelography, represents the best means of obtaining an accurate estimate, roentgenologically, of the condition of the upper part of the urinary tract. The serial pyelograph has the following advantages: It is inexpensive, interchangeable with the Bucky diaphragm tray and adaptable to most of the Bucky diaphragms now in use. Moore stated that in a review of 211 cases its use was shown to enhance greatly the proper interpretation of pyelograms. Evidences of motility in the calices, pelvis and ureter are easily demonstrated. Constant filling defects from shadowless obstructions are more apparent, and the identification of suspicious shadows is facilitated. There is also evidence with this method that the obstruction often noted on the passage of a bulb through the ureter and the "hang" felt on its withdrawal are often caused by local spasm rather than by stricture of the ureter.

Herbst<sup>57</sup> reported the effect of renal sympathectomy on the motility of the upper part of the urinary tract as observed by means of urography and pyeloscopy. The indications for renal sympathectomy are reflex anuria, nephralgia, early renal tuberculosis, the prevention of reforma-

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55. Liberson, F.: Deep X-Ray Therapy in the Treatment of "Painful Heel" with Report of Thirty-One Cases, *J. Urol.* **28**:105 (July) 1932.

56. Moore, T. D.: The Value of the Serial Pyelograph in Diagnosis, *J. Urol.* **28**:437 (Oct.) 1932.

57. Herbst, W. P.: Pyeloscopic and Urographic Study Before and After Renal Sympathectomy, *J. A. M. A.* **99**:2004 (Dec. 10) 1932.

tion of renal calculi, certain types of nephritis, acute hypertension, renal sympathicotonia, painful hyperdynamic motility of the renal pelvis and painful nephroptosis. Pyeloscopy is, at present, the most satisfactory means of studying the myoneural dynamics of the upper part of the urinary tract in all such painful conditions.

Herbst described a painful abnormal motility syndrome which he called hyperdynamic motility of the renal pelvis which is relieved only by renal sympathectomy. Sympathectomy changed the mechanism from one of hyperdynamic motility to one of abnormally decreased activity. The decreased motility continued only about eight months, at which time hypermotility reappeared. The observations were interpreted to indicate that the interrupted nerve paths were beginning to be reestablished. In this case the resumption of the hyperactivity had not been accompanied by recurrence of pain.

The fact that recognition of various painful abnormal motility syndromes by pyeloscopy is practical will make the classification of painful renal conditions more accurate and should result in a more widespread utilization of this valuable aid in diagnostic roentgenology.

Wesson<sup>58</sup> stated that a comparison has been made of the relative merits of skiodan iopax and an iopax derivative. The last-mentioned preparation was found to be most satisfactory because of the sharpness of the pictures, the absence of untoward reactions and the ease of administration. The best pictures obtained with the iopax derivative were usually made after five minutes.

In the majority of cases of pyelitis in infancy, intravenous injections were found to be valueless because there was no excretion of the medium. Intravenous urography should be the first diagnostic procedure in cases in which rupture of a kidney, ureter or bladder is suspected.

Wesson stated that in cases of chronic ureteral stones that partially block the ureter, a well outlined pelvis secondary to stasis and a varying grade of hydronephrosis is shown. A ureteral catheter in the pelvis may cause inhibition of secretion of the intravenous medium. Intravenous urography is merely one diagnostic procedure, and the findings should be checked, as far as possible, by retrograde methods. This procedure has, more or less, restored a large field of medicine to the general practitioner, but it must be realized that the procedure is just another diagnostic adjunct, and that the urologist must still be depended on for the final diagnosis.

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58. Wesson, M. B.: Intravenous Urography: A New Diagnostic Procedure for the General Practitioner, *Urol. & Cutan. Rev.* **36**:296 (May) 1932.

Cumming and Jarre<sup>59</sup> stated that roentgen signs of infections of the urinary tract have been arranged to parallel, as closely as possible, the logical sequence of the classification of infections. Their reports are based on data accumulated over a period of three years of study with the Cinex camera of Jarre.

The authors concluded from their experience that the transport mechanism of the upper part of the urinary tract, and even of the bladder, has been shown to conform to a regular physiologic order of peristaltic emptying. It is dependent on innervation of both extrinsic and intrinsic origin. The renal pelvis, its calices acting more or less independently of one another, contracts segmentally, the pelvis itself contracting and resting in true systole and diastole. The ureter contracts in orderly fashion, there being three main segmental units. These are regularly affected by disease processes, as are the integral parts of the pelvis itself. Acute infections of the mucosal structures are irritative first and paralytic later, and gradually, in chronic stages, tend to produce atony. Edema of the mucosa of the urinary tract causes poor delineation of the borders of calices, pelvis and ureter, especially in intravenous urographic examinations.

The various types of infection of the upper part of the urinary tract manifest themselves from the standpoint of roentgen ray observations in certain more or less fixed deviations from what has been established as normal physiologic activity. Various types of infection give evidence of no differentiating urographic symptoms.

*Resection of the Presacral Nerve.*—Foulds<sup>60</sup> stated that the recent advances in surgery of the sympathetic nervous system have been applied to diseases of the urinary bladder. Knowledge of the exact anatomy of the nerve supply and the neurophysiology of the bladder has been limited until the anatomic studies of Latarjet and Bonnet in 1913 and later of Laux, Pieri and others. Learmonth has recently applied the anatomic data of these French investigators clinically to the relief of some of the forms of neuromuscular dysfunction of the bladder.

The bladder and its sphincters receive their nerve supply from three sources: first, the hypogastric nerves, the thoracolumbar outflow of the sympathetic system through the presacral nerves whose division constitutes the hypogastric nerves; second, the pelvic nerves or *nervi erigentes*, the sacral autonomic fibers, and third, the pudic nerves from the somatic centers in the sacral part of the cord.

59. Cumming, R. E., and Jarre, H. A.: Roentgen Symptomatology of Infected Urinary Passages in Combination with a Classification of Urinary Tract Infections. *J. Urol.* **28**:455 (Oct.) 1932.

60. Foulds, G. S.: Resection of the Presacral Nerve in Urological Cases, *Brit. J. Surg.* **20**:139 (July) 1932.

Micturition involves a diphasic neuromuscular mechanism; the phase of filling, which is involuntary and requires relaxation of the bladder, with contraction of the internal sphincter, and the phase of emptying, which is under voluntary control and involves contraction of the vesical muscles or detrusor fibers and relaxation of the sphincter.

The phase of filling is dependent on motor impulses through the hypogastric nerves which produce a contraction or state of tonus in the sphincter and inhibitory impulses to the vesical muscle. The hypogastric nerves also carry afferent fibers to the bladder, which transmit sensory impulses, chiefly those of overdistention, with suprapubic discomfort. The emptying or detrusor phase of vesical action is under the control of the pelvic nerves (*nervi erigentes*), which carry efferent motor stimuli to the detrusor muscles and motor inhibitory impulses to the internal sphincter. These nerves also carry a large proportion of the sensory fibers from the bladder. The pudic nerves carry motor impulses to the compressor urethral muscles and sensory fibers to the deep urethra.

In cases of neuromuscular dysfunction of the bladder in which there is imbalance between the sacral autonomic and sympathetic outflow, the latter may be disconnected by section of the presacral nerve. It is accessible at the point where it crosses the left iliac vein.

Pieri was the first to point out the possibility of relieving pain, in some vesical lesions, by this operation. Learmonth has reported 4 cases in which relief was obtained by operation: in 3 cases for panmural ulcerative cystitis and in 1 case for tuberculous cystitis. Not only is there relief of pain, but the vasodilatation may produce a curative effect on the vesical lesion. Learmonth has also reported 2 cases of sympathetic-parasympathetic imbalance due to lesions of the cord below the origin of the sympathetic outflow, with spasm and overaction of the internal sphincter, in which good results were obtained by presacral neurectomy.

Foulds reported a case of this type. His patient had a fracture dislocation of the second lumbar vertebra with residual urine, incontinence and inability to empty the bladder except by action of the accessory muscles and pressure over the lower part of the abdomen.

Transmission of detrusor impulses through the pelvic nerves was not rendered completely impossible, as was indicated by the returning power of erection and the possibility of some sphincteric relaxation if enough time was taken. However, the "brake" action of the sympathetic nerves was too strong for the weakened detrusor forces of the sacral autonomic impulses.

Section of the presacral nerve was followed by relief of suprapubic discomfort when the bladder was distended, by gradual reduction of the quantity of residual urine to 60 cc. and by elimination of overflow

incontinence. There was some loss of sphincteric control which was exercised entirely by the external sphincter, but this could be regulated by care.

[COMPILERS' NOTE.—Elaut<sup>61</sup> has recently made an exhaustive study of the anatomy of the presacral nerve. He has found that it is never "presacral" but "prelumbar" because it divides, shortly after its origin, at the aortic bifurcation, into the hypogastric nerves which run to the side wall of the pelvis and which are always distinct entities at the level of the promontory of the sacrum. Sometimes the right hypogastric nerve may cross the concave surface of the sacrum, but the so-called presacral nerve itself never does. It is exceptional to find a true nerve, and in a high percentage of cases it is merely a plexus. In 8 per cent of cases, the pelvic mesocolon is inserted exactly in front of the interiliac trigone, so that the nerve cannot be reached by simple incision of the peritoneum. In such cases the chief branches of the inferior mesenteric artery must be moved to the left so as to expose the triangular space between the two common iliac arteries.]

#### ENURESIS

Campbell<sup>62</sup> stated that there are many definitions of enuresis. His definition is the unintentional or involuntary nocturnal or diurnal urination in the absence of demonstrable uropathy. This includes only the so-called functional cases.

In a series of 249 children, 4 years of age and older, whose condition had been diagnosed enuresis and for whom physical therapy or psychotherapy had failed, complete urologic examinations were carried out. Normally, control of the bladder should be established by the age of 2½ years, and with few exceptions children of this age should go all night without urination.

Campbell carefully noted the amount of residual urine. It is one of the most important findings in this series, and a point which has not been emphasized by other observers, that residual urine is commonly present among patients with enuresis. Residual urine was found in 16 per cent (40 cases, or in a ratio of 1:6), and varied from 10 cc. to more than 300 cc. The average amount was between 25 and 45 cc. With this residual urine the neck of the bladder is continually irritated, and less filling of the bladder is required to cause the conscious desire to void. Injury to the upper part of the urinary tract by back-pressure

61. Elaut, L.: *Surgical Anatomy of So-Called Presacral Nerve*, Surg., Gynec. & Obst. **55**:581 (Nov.) 1932.

62. Campbell, M. F.: *Enuresis: Its Urologic Aspects*, J. Urol. **28**:255 (Sept.) 1932.

regularly occurs with intravesical obstruction and residual urine; its effect on the kidney is of prime concern.

Campbell stated that the next procedure in the investigation is cystometry. A small catheter is introduced into the empty bladder and, through a three-way stopcock, is connected with a graduated reservoir on the one hand and a manometer on the other. Definite volumes of fluid (potassium permanganate) are introduced into the bladder and the intracystic pressure is recorded. In his experience with cystometric studies of 172 patients with enuresis, only now and then did he find the observation of diagnostic aid. In half of the cases cystometric values were normal, in a fourth they were indicative of a hypertonic state, and in a fourth, of a hypotonic state.

A plain roentgenogram of the genito-urinary tract is made for possible shadows of stones but more particularly for spinal defects, notably spina bifida (occulta) which is said to be of unusually high incidence among children with enuresis. Among 237 cases, 201 of the roentgenograms gave evidence of a normal condition; 34 (14.3 per cent) of spina bifida occulta and 2 of sacral deformity. In 1 case, congenital sacral deviation to the right was accompanied by motor and sensory loss of the sacral nerves, with vesical and rectal incontinence. Following a plain roentgenogram, a cystogram was made by filling the bladder to the point of moderate distention with a radiopaque solution. The child was then subjected to cystoscopy. In 85 per cent of these cases, examination was performed without general anesthesia. Cystoscopic examination disclosed practically every known lesion of the urinary tract: stone, tuberculosis, all gradations of cystitis, prostatitis, verumontanitis, infections of the upper part of the urinary tract, neuromuscular disease of the vesical outlet, congenital contracture of the vesical neck, posterior urethral valves, urethral stricture and many others. Congenital atresia of the meatus is the most common stricture, and in a large number of cases has been found to be the entire cause of enuresis. Frequently, the tight meatus becomes ulcerated. Regularly, there is urinary back-pressure behind the obstruction, sometimes with considerable injury of the proximal channels, especially the bladder. Campbell stated that he had not observed enuresis due to phimosis, but that several children had been seen in whom enuresis followed circumcision—unquestionably a psychic disturbance.

Among girls, a high incidence of urethrotrigonitis has been found, involving the posterior part of the urethra and the anterior part of the trigone. The mucosa is intensely congested, often granular and not infrequently edematous. The condition usually responds admirably to the treatment employed for women, namely, urethral dilation and the application of silver nitrate, either topically or by catheter.



Campbell concluded that in most cases treatment is based on the urologic diagnosis; sometimes radical operation is required. By these various urologic therapeutic procedures, further destruction of the urinary tract can be prevented, and often underlying disease is cured; incidentally, the enuresis ceases. One may be assured that when there is no demonstrable pathologic change in the urinary tract, normal vesical control will be established ultimately.

#### INFLUENCE OF GYNECOLOGIC CONDITIONS ON THE GENITO-URINARY TRACT

Stein and Rodgers<sup>63</sup> stated that roentgenologic examinations were undertaken with the idea of demonstrating, if possible, a relationship between changes along the urinary tract of women which are based on pathologic conditions, such as fibroid tumors or ovarian cysts arising in the pelvis. To accomplish their purpose, they decided on simultaneous intravenous injections of skiodan and transuterine injections of iodized poppy seed oil 40 per cent.

The cases in which examination has been made thus far can be classified in two groups: those of pregnancy and those of pathologic pelvic tumor. In 11 cases injection was by this method; 5 of the patients were pregnant, and the period of gestation varied from six weeks to six months. In all cases of pregnancy, even as early as six weeks, there is dilatation of both ureters, this dilatation increasing with the period of gestation. On the other hand, with uterine myomas of a corresponding size, similar dilatation of neither the renal pelves nor the ureters was found. Stein and Rodgers state their belief that dilatation of the ureters in pregnancy is a purely physiologic process, whereas a pelvic tumor of a corresponding size, whether fibroid or cystic, is incapable of producing a similar dilatation by mechanical means alone.

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63. Stein, Arthur, and Rodgers, Mortimer: The Influence of Gynecological Conditions on the Genito-Urinary Tract as Shown by Simultaneous Injections of Skiodan or Uroselectan (Intravenously) and Lipiodol: Preliminary Report, *Surg., Gynec. & Obst.* 55:490 (Oct.) 1932.

## CHRONIC SUBDURAL HEMATOMA

### ETIOLOGY AND TREATMENT

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OMAHA

The subject of chronic subdural hematoma has been presented in an excellent manner in recent years by several writers (Putnam and Cushing,<sup>1</sup> Rand,<sup>2</sup> Grant,<sup>3</sup> Holmes,<sup>4</sup> Brodie,<sup>5</sup> Sherwood,<sup>6</sup> Jelsma<sup>7</sup> and Dandy<sup>8</sup>), and this clinical entity is well known. The object in this paper is to contribute some observations on the source of the bleeding from the cerebral veins which cross the subdural space to enter the superior longitudinal sinus, and to add the reports of five cases in which drainage through a trephine opening was used in treatment.

The primary etiologic factor of chronic subdural hematoma is now generally recognized to be trauma to the head and the source of the bleeding, venous. The character of the injury to the head, however, is often so mild as to escape even the notice of the patient, particularly since symptoms of compression of the brain do not appear for several weeks or months after the injury. These peculiarities have clouded the picture and have led to various interpretations of the exact source and mechanism of the slow or recurrent accumulation of blood.

There also has been considerable confusion in the differentiation of traumatic chronic subdural hematoma from the nontraumatic pachymeningitis interna hemorrhagica which Virchow<sup>9</sup> first named in 1857

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1. Putnam, T. J., and Cushing, H.: Chronic Subdural Hematoma, *Arch. Surg.* **11**:329 (Sept.) 1925.
2. Rand, C. W.: Chronic Subdural Hematoma; Report of 7 Cases, *Arch. Surg.* **14**:1136 (June) 1927.
3. Grant, F. C.: Chronic Subdural Hematoma, *Ann. Surg.* **86**:485 (Oct.) 1927.
4. Holmes, W. H.: Chronic Subdural Hemorrhage, *Arch. Neurol. & Psychiat.* **20**:162 (July) 1928.
5. Brodie, F.: Delayed Subdural Hemorrhage, *Canad. M. A. J.* **20**:273 (March) 1929.
6. Sherwood, D.: Chronic Subdural Hematoma in Infants, *Am. J. Dis. Child.* **39**:980 (May) 1930.
7. Jelsma, F.: Chronic Subdural Hematoma, *Arch. Surg.* **21**:128 (July) 1930.
8. Dandy, W. E.: Subdural Hematoma, in Lewis, Dean: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, 1932, vol. 12, p. 295.
9. Virchow, R.: *Haematoma durae matris*, *Verhandl. d. Phys.-med. Gesellschaft. Würzburg* **7**:134, 1857.

and interpreted as being of inflammatory origin. He described a progressive lesion, most commonly found in asylum material and associated with cerebral atrophy, in which the formation of a very vascular subdural membrane was apparently followed by ecchymoses and subdural hemorrhage. This membrane varied in thickness, but typically measured a few millimeters and showed lamellations of blood clot on its inner surface in the more chronic cases. Virchow did not present comparative studies of traumatic subdural hematoma, which he recognized chiefly in the new-born, but thought that it was unlikely for a primary hemorrhage to produce the pathologic condition described by him.

This concept of the spontaneous inflammatory origin of such senile hemorrhagic subdural membranes gained wide acceptance and still serves to differentiate pachymeningitis interna hemorrhagica from traumatic chronic subdural hematoma (Dandy<sup>8</sup>). A comparative study of the two membranes was made by Putnam and Cushing,<sup>1</sup> who described an essentially vascular type and a reactive type of membrane in which "the gross appearance of these two forms is practically identical and the microscopic pictures so similar that they are easily confused." The chief histologic difference was the presence of large mesothelial-lined spaces in the traumatic membrane and of larger thin-walled blood vessels in the spontaneous membrane.

The recognition of trauma as a cause of chronic subdural hematoma dates back to early reports (Schuberg<sup>10</sup>), although its significance was often overlooked owing to delayed symptoms, and traumatic cases undoubtedly were included in descriptions of the spontaneous form. Brion,<sup>11</sup> Bowen,<sup>12</sup> Kasemeyer,<sup>13</sup> and Henschen<sup>14</sup> made notable contributions to the incidence and symptoms of traumatic subdural hemorrhage. A number of writers, (Baillarger,<sup>15</sup> Hewitt,<sup>16</sup> Sperling,<sup>17</sup> Hue-

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10. Schuberg, W.: *Das Haemtaoma durae matris bei Erwachsenen*, Virchows Arch. f. path. Anat. **16**:464, 1859.

11. Brion, W.: *Die operative Behandlung der intraduralen Blutungen traumatischen Ursprungs*, Inaug. Diss., Strassburg, 1896.

12. Bowen, W. H.: *Traumatic Subdural Haemorrhage*, Guy's Hosp. Rep. **59**: 21, 1905.

13. Kasemeyer, E.: *Ueber post-traumatische Pachymeningitis unter dem Bilde der post-traumatischen Neurose und über deren unfallgerichtliche Bedeutung*, Friedrich's Bl. f. gerichtl. Med. **62**:293, 339, 401, 1911.

14. Henschen, K.: *Diagnostik und Operation der traumatischen subduralen Blutung*, Arch. f. klin. Chir. **99**:67, 1912.

15. Baillarger, M.: *Du siège de quelque hémorrhagies méningées*, Thèse de Paris, 1837.

16. Hewitt, P.: *On Extravasations of Blood into the Cavity of the Arachnoid*, Tr. Med.-Chir. Soc. London **28**:45, 1845.

17. Sperling, H.: *Ueber Pachymeningitis haemorrhagica interna*, Inaug. Diss., Königsberg, 1872.

genin,<sup>18</sup> Wigglesworth<sup>19</sup> and Robertson<sup>20</sup>) questioned the primary inflammatory origin of the membrane in the spontaneous form and believed that it was the result of primary extravasation of blood into the subdural space. The cause of this bleeding was variously attributed to venous congestion, "dry-cupping" from cerebral atrophy, degenerated blood vessels and various systemic conditions or diseases of the blood. The source of the bleeding in traumatic subdural hematoma was thought to be torn meningeal vessels, supplemented by later bleeding from the lining membrane, to account for its chronic and recurrent course.

A most illuminating paper on the subject of traumatic subdural hematoma and its relation to pachymeningitis hemorrhagica by Trotter<sup>21</sup> appeared in 1914, which, as stated by Cushing,<sup>1</sup> almost had escaped attention during the period of the war. And even in this comprehensive paper by Putnam and Cushing,<sup>1</sup> it does not seem that enough attention was given to Trotter's<sup>21</sup> statements concerning the source of the hemorrhage. Since these statements can hardly be improved on, and apply particularly to case 1 of this report, it may be permissible to quote at length:

It is nearly certain that the cerebral veins passing from the brain to the tributaries of the superior longitudinal sinus are always the source of the blood. They are short trunks passing direct from brain to dura nearly at right angles to each. Such a vein has its cranial end firmly fixed by the rigid dura, while its cerebral end is attached to the comparatively movable hemisphere. Between these two points the vein passes directly, with no tortuosity to allow for possible movement of the brain. The morbid anatomy of contusion by contre-coup shows that considerable movement of the brain is possible within the skull as the result of external violence.

It is, however, characteristic of chronic subdural hemorrhage that the history of injury which has preceded the development of symptoms is usually not a striking feature of the case, and may be withheld unless specifically inquired for. Severe violence is not the kind of injury we should expect to produce the required lesion, viz., the uncomplicated rupture of one or two delicate veins. Such a trauma would be liable to complicate the condition with gross laceration or contusion of the brain, and produce conditions antagonistic to the slow or intermittent oozing required. On the other hand, comparatively slight violence favourably directed to produce an adequate displacement of the brain and nothing else, would give just the necessary conditions. It is obvious that the falx protects the brain from transverse displacement at the very place where it is most necessary to avoid displacement; at the same time, anteroposterior movement is not equally guarded against, and there can

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18. Huegenin, O.: Inflammation of the Dura Mater, in von Ziemssen, Hugo Wilhelm: *Cyclopedia of Practice of Medicine*, American Translation, New York, W. Wood & Co., 1877, vol. 12, p. 386.

19. Wigglesworth, J.: Remarks on the Pathology of the So-Called Pachymeningitis Interna Haemorrhagica, *Brain* 15:431, 1892.

20. Robertson, G. M.: The Formation of Subdural Membranes, or Pachymeningitis Haemorrhagica, *J. Ment. Sc.* 39:203, 1893.

21. Trotter, W.: Chronic Subdural Hemorrhage of Traumatic Origin and Its Relation to Pachymeningitis Haemorrhagica Interna, *Brit. J. Surg.* 2:271, 1914.

be little doubt that a sharp blow on the front or back of the head can comparatively easily produce a good deal of dislocation of the hemispheres, which of course would be equal on the two sides. It is interesting to notice that in all of my cases the violence had been quite moderate—in one of them extremely so,—that in three there was good reason to believe the blow had been on the front or back of the skull, and that in two the hemorrhage was bilateral.

I can amplify this conception of the source and mechanism of the bleeding in chronic subdural hematoma only by the report of a clinical case in which intermittent bleeding from an opening in the superior longitudinal sinus actually was seen during an operation two and one-half months after the primary injury of the head.

*CASE 1.—History.*—H. P. S., a man, aged 29, entered the Nebraska Methodist Hospital, on April 19, 1928. He was referred by Dr. G. A. Young, with a diagnosis of chronic subdural hematoma. The patient had been in an automobile accident about Feb. 1, 1928, and had sustained severe lacerations of the right frontotemporal part of the scalp; but there had been no loss of consciousness, vomiting or other recognized injury, and he returned promptly to work. One week or ten days later he began to have headache and pain in his right ear, which discharged purulent material. These symptoms continued for about a week and then disappeared, except for occasional headache, on account of which he did not work. About April 1, 1928, there was a severe headache for ten days, associated with pain in the right hip and thigh. This disappeared, and on April 15, 1928, there occurred a short interval when the right hand seemed weak and useless, and he was unable to speak the words he wished to use. This was accompanied by a severe headache and projectile vomiting. These same symptoms recurred on the following day and continued for a longer time.

*Examination.*—Neurologic examination on April 19, 1928, showed that the cranial nerves were normal except for a slightly diminished left olfactory sense. The upper extremities were normal, the abdominal and cremasteric reflexes active and the lower extremities normal. A spinal puncture showed a pressure of 24 mm. of mercury with jugular compression response, a colorless fluid, 10 cells, a normal amount of protein, a negative Wassermann test and a normal colloidal gold curve. A preoperative diagnosis of a left parietal tumor, suspected to be chronic subdural hematoma, was made.

*Operation.*—On April 23, an exploratory trephine in the left parietal region was done with the patient under local anesthesia. A dark, slightly adherent membrane was found beneath the dura, with no pulsation. Needle aspiration withdrew very dark blood which did not clot readily on standing. The membrane was opened; a large quantity of old blood escaped, and the cavity was irrigated with physiologic solution of sodium chloride until it returned clear. A few small clots came out. The cavity was seen to extend chiefly anteroposteriorly and medially. A rubber tissue drain was placed in the opening to permit gradual restoration of the markedly compressed cerebral hemisphere.

*Course.*—The patient was much improved for twenty-four hours following this operation, but pain in his head recurred the following afternoon, with restlessness, stupor and a convulsion at 3:30 a. m., on April 25. A discharge of fresh blood appeared on the head dressings, and a diagnosis of recurrent hemorrhage was made. He was taken to the operating room, and a left parietal bone flap was turned down. A similar dural flap was made, leaving the cyst wall intact, except

at the previous opening, which was plugged with blood clot. On the incision of the cyst a considerable amount of liquid blood and air escaped. The large cavity was washed out with physiologic solution of sodium chloride and a good view was obtained of its interior, which extended the full length of the skull and had compressed the cerebral hemisphere fully 3 cm. At first the wall appeared to contain no bleeding point, but when the patient began to strain from vomiting, dark blood was seen to escape intermittently from a place well forward on the superior longitudinal sinus, beneath the glabella. During a period of one half hour this place was watched, and an attempt was made to close the opening with a piece of muscle. Bleeding occurred only when the patient strained and not after the muscle was applied. The opening was a considerable distance forward and was reached with difficulty from the parietal opening. A frontal bone flap was desired for better exposure, but since no more bleeding occurred and the patient's condition from loss of blood and operative shock was not good, further work did not seem advisable. A rubber tissue drain was placed well forward over the hemisphere, and the bone flap was replaced. The patient was improved in reaction for a few hours, but fresh blood again appeared on the dressings, and he became comatose, indicating further bleeding. He was taken to the operating room, and a triangular piece of bone was elevated in the left frontal region, directly over the bleeding point. Blood clot and active intermittent bleeding were found again coming from the superior longitudinal sinus, where an anterior cerebral vein must have been torn out at the time of the injury. This opening was closed by silver clips and electrosurgical coagulation. The cerebral hemisphere this time appeared much larger, indicating more active replacement of tissue fluid. It was hoped that this final closure of the venous opening would result in recovery, but the patient did not regain consciousness and died the following day after gradually rising temperature and pulse and respiratory rates not relieved by dehydration therapy. Postmortem examination was not permitted.

This case presents the unique observation of a persisting opening in the superior longitudinal sinus which evidently was the source of the large subdural hematoma found at operation, two and one-half months after a mild injury of the head. It confirms the generally accepted concept of the origin of this lesion from ruptured cerebral veins as they cross to enter the sinus, and explains the slow and intermittent accumulation of blood which has seemed necessary to produce the clinical symptoms. The unfortunate outcome was due to the unusual persistence of this opening, leading to postoperative hemorrhage, to the inaccessible location of the opening from a parietal bone flap and to postoperative edema of the brain.

The latent interval, with gradual or intermittent accumulation of blood or serum in subdural hematoma, has long been a puzzling feature of the condition. Most writers, following Virchow's<sup>9</sup> lead, have assumed repeated ruptures of thin-walled blood vessels in the lining membrane. Gardner<sup>22</sup> recently has offered experimental evidence that cerebrospinal fluid is drawn into the sac through the arachnoid by

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22. Gardner, W. J.: Traumatic Subdural Hematoma; with Particular Reference to the Latent Interval, *Arch. Neurol. & Psychiat.* **27**:847 (April) 1932.

osmosis. Both of these factors may play a part, but the demonstrated intermittent bleeding from the superior longitudinal sinus in the preceding case would seem to be a more logical explanation to account for the major portion of the accumulated contents of the sac.

A few added deductions in support of Trotter's<sup>21</sup> conception of the origin of chronic subdural hematoma might be presented. Our present knowledge of posttraumatic edema of the brain indicates that injuries of the head severe enough to produce even transient unconsciousness are liable to be followed by appreciable signs of edema of the brain. This tends to compress the subarachnoid and subdural spaces by swelling of the brain and would favor closure of any torn veins long enough for a firm thrombus to form and prevent extensive or recurrent bleeding. The absence of edema of the brain following the mild injury of the head in which simple displacement of the brain occurs, as in the frontal or occipital bump, might permit subdural venous bleeding. The added factors of normal activity and straining following the injury to the head and the rigid wall of the opening in the superior longitudinal sinus would favor continued intermittent bleeding.

Following this reasoning a little farther offers an explanation of the observed frequency of chronic subdural hematoma in conditions of cerebral atrophy (Bowen<sup>12</sup>). It is a common postmortem observation in such cases, and now frequently seen in encephalograms (fig. 1), that the retracted cerebral hemispheres appear suspended at their medial borders by the venous connections to the superior longitudinal sinus. This condition, combined with the mild blows on the head which these patients commonly suffer or the venous congestion from straining, coughing or convulsions, would favor rupture of these venous connections and permit free subdural hemorrhage. Trotter<sup>21</sup> likewise emphasized these factors as a possible explanation of spontaneous subdural hemorrhage in conditions of cerebral atrophy.

It is not contended on the basis of this single case that all subdural hematomas arise from bleeding from the superior longitudinal sinus. Many other sources are possible, one of which was excellently portrayed in Rand's<sup>2</sup> paper as being a ruptured large cerebral vein over the convexity of the hemisphere. Middle meningeal subdural hemorrhage may persist without operation for many weeks, as was suspected in case 4 of this report. A cerebral aneurysm may rupture at the base of the brain into the subdural space and produce a large and rapidly fatal subdural hematoma, as was reported by Bennett and myself.<sup>23</sup> Birth injury may give rise to subdural hemorrhage over the tentorium. But rarely would any of these traumas produce the clinical and pathologic condition of chronic subdural hematoma.

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23. Keegan, J. J., and Bennett, A. E.: Cerebral Aneurysm and Cortical Herniation, *Arch. Neurol. & Psychiat.* **26**:36 (July) 1931.

The treatment of chronic subdural hematoma has varied greatly, often depending on the neurosurgical qualifications of the operator or the serious condition of the patient which did not permit an extensive operation. However, guided by Virchow's<sup>9</sup> conception of the etiologic significance of the lining membrane and Putnam and Cushing's<sup>1</sup> recommendation, an osteoplastic flap and thorough removal of the membrane generally have been advocated (Rand<sup>2</sup> Grant<sup>3</sup> Jelsma<sup>7</sup> and Dandy<sup>8</sup>). Fortunately not all patients have been subjected to this major procedure, and an increasing number of satisfactory recoveries have been reported after simple evacuation through a trephine opening.



Fig. 1.—Encephalogram of a patient with chronic epilepsy, showing cerebral atrophy and suspension of the cerebral hemispheres by venous connections to the superior longitudinal sinus.

Two recent critical surveys of methods of treatment by Fleming and Jones<sup>24</sup> and McKenzie<sup>25</sup> definitely have favored the simpler procedure and called attention to the similar recommendation of Trotter<sup>21</sup> in 1914. I am in agreement with this conservative method of treatment and have applied it in my cases with reasonable success. The problem, however, is not quite so simple that a fixed rule can be applied to all

24. Fleming, H. W., and Jones, O. W., Jr.: Chronic Subdural Hematoma, *Surg., Gynec. & Obst.* **54**:81 (Jan.) 1932.

25. McKenzie, Kenneth G.: A Surgical and Clinical Study of Nine Cases of Chronic Subdural Haematoma, *Canad. M. A. J.* **26**:534 (May) 1932.



cases. Each must be considered in the light of both preoperative and postoperative findings; the presence or absence of organization in the hematoma which may favor delayed resolution and epilepsy; the size and duration of the lesion which may caused delayed obliteration of the cavity or predispose to postoperative edema of the brain; the danger of recurrent hemorrhage as in case 1, and the persistence of a low grade pressure syndrome which may require decompression for relief as in case 2 (fig. 2).

From my limited experience and deduction from the literature, I should favor the following procedure in treatment. In all cases of sus-



Fig. 2 (case 2).—Encephalogram taken in a case of right subdural hematoma occurring six weeks after trephine drainage.

pected chronic subdural hematoma, exploration should be made through a small lateral frontal or parietal trephine, which can be made a part of a large frontoparietal bone flap if necessary. Simple evacuation by suction and irrigation with physiologic sodium chloride with rubber tissue drainage for forty-eight hours should be the preliminary procedure, unless dense organization of the clot is found. Moderate dehydration therapy by limitation of fluid, magnesium sulphate catharsis or intravenous injection of a hypertonic solution of dextrose should follow the operation for a few days to counteract the tendency toward edema of the brain. Most patients probably will recover satisfactorily under this conservative regimen. A bone flap is indicated to remove an organized thrombus or to find the source of a recurrent hemorrhage, but not for

removal of the ordinary thin protective membrane surrounding the hematoma. This membrane will disappear within a few months, as in a case reported by Horrax and quoted in McKenzie's<sup>25</sup> paper, or become insignificant as in case 2 of this report (fig. 3). Drainage for forty-eight hours would seem to be indicated both to allow the escape of some retained blood and to permit the escape of fluid and air as the markedly compressed brain gradually is restored to normal volume. A subtemporal decompression might well be made a part of the original operation to allow for some unavoidable postoperative pressure from edema of the brain, or to relieve a low grade chronic pressure syndrome from arachnoiditis as in case 2. The possibility or even the probability of a bilateral hematoma, as emphasized by Trotter<sup>21</sup> and by Fleming and Jones,<sup>24</sup> always should be kept in mind and bilateral trephine exploration done on the slightest evidence. Double trephine openings as advocated by Fleming and Jones<sup>24</sup> probably are not necessary, although they add little hazard to the operation and perhaps insure more complete evacuation of the hematoma.

#### SUMMARY

The primary etiology of chronic subdural hematoma is mild trauma to the head, and the source of the bleeding is torn veins which connect the cerebral hemispheres with the superior longitudinal sinus.

Edema of the brain following severe injury of the head compresses torn veins, favors clotting and prevents large subdural accumulation of blood.

The latent period and intermittent bleeding are demonstrated by the case reported to be due to a persisting opening in the superior longitudinal sinus.

Cerebral atrophy causes suspension of the cerebral hemispheres by their venous connections to the superior longitudinal sinus and makes these patients more susceptible to subdural hemorrhage.

Trephine exploration and drainage should be used in treatment, unless specific indications call for more radical surgical procedures.

**CASE 2.—History.**—P. R., a man, aged 24, entered the Jennie Edmundson Hospital, Council Bluffs, Ia., on Nov. 9, 1931. He was referred by Dr. S. D. Maiden, with a diagnosis of intracranial pressure. This patient was in an automobile collision on July 19, 1931. He suffered no serious injury, was not aware of any injury of the head, and did not lose consciousness. Two days later he began to have frontal and temporal headache, which persisted and gradually became worse. On September 1, rather severe intermittent pain in the right frontal area developed, for which he consulted a specialist in diseases of the nose and throat. Cocainization of the right nares relieved the pain. There was no choked disk at this time. The pain recurred, and the right maxillary antrum was drained on September 14, with some relief. He returned in a few days with a history of an attack of transient weakness or dead feeling in his left arm. Examination of the fundus showed a

papilledema of 4 diopters with hemorrhages. The visual fields showed some color restriction but no segment defect. The spinal fluid pressure was 18 mm. of mercury; there were 10 cells and the fluid was colorless.

*Examination.*—Neurologic examination, on September 21, showed a questionable weakness of the left side of the face and of the tongue; otherwise the reactions to motor, sensory, reflex and coordination tests were normal. The tendon reflexes were slightly sluggish; the abdominal and cremasteric reflexes, active. The patient appeared apathetic and yawned frequently, although he was responsive and rational. There were: a low grade fever, a leukocyte count of 17,000, with 88 per cent polymorphonuclears, a pulse rate of 74 and a blood pressure of 130 systolic and 70 diastolic. There was no history of suppuration of the ear or sinus trouble, but a peritonsillar abscess had been lanced in July, 1930, and the patient had not felt entirely well since. With this history suggestive of infection, and the patient's positive statement that he had not injured or struck his head in the automobile accident, the preoperative diagnosis favored right frontal abscess rather than hematoma. An exploratory trephination was done in the right lateral frontal region on September 22, and a dark bluish membrane, characteristic of chronic subdural hematoma was encountered. Two or 3 ounces (56 to 85 Gm.) of dark liquid blood was removed by suction, and a rubber tissue drain was left inserted in the cavity, one drain extending into the temporal fossa where evacuation did not seem complete. The drains were removed after forty-eight hours; there was moderate drainage of old blood during the first twenty-four hours.

The patient promptly improved in alertness and was relieved of pain, although for a few days he complained of an occasional sensation of numbness in his left hand. Headache occurred on October 14, and vision seemed slightly blurred. A choked disk of 4 diopters persisted. The cisternal cerebrospinal fluid pressure was 22 mm. of mercury; 30 cc. of fluid was removed, the pressure being reduced to 8 mm. The patient felt relieved after this drainage, but symptoms recurred in about a week and cisternal pressure of 18 mm. was found; 25 cc. of fluid was removed on October 21. The papilledema had subsided to 2 diopters, and vision was better. On Oct. 28, cisternal pressure was 12 mm., and 25 cc. of fluid was removed. The pressure seemed to be subsiding, but on Nov. 2, it rose to 20 mm. again, and the patient complained of frontal headache and pain in his eyes. He did not feel well and had not regained normal physical and mental reactions.

*Second Admission.*—He was admitted to the Nebraska Methodist Hospital on November 9, for an encephalogram, to determine the presence of a suspected residual hematoma. Before the injection of air a needle was inserted through the old trephine opening, and no fluid was obtained. The encephalogram showed a partial obliteration of the subarachnoid spaces over the right hemisphere and slight displacement of the ventricles to the left, with asymmetrical dilatation of the ventricles, more pronounced on the left. The findings indicated an obliterative pressure lesion over the lateral surface of the right hemisphere. A needle was inserted through the old trephine opening in search of old blood, but nothing was found. From this it was interpreted that there probably was a walled-off hematoma in the right temporal fossa where evacuation was imperfect at operation.

The patient was allowed to go home, and felt considerably improved for two weeks following the encephalogram. Cisternal pressure was found to be normal on November 18, but the patient returned to the hospital on November 25, with headache and pain in his eyes again and a pressure of 18 mm. of mercury. Symptoms and an increased intracranial pressure of 14 mm. persisted until December 2, and operation was advised.

*Operation and Course.*—At this operation, Dec. 3, 1931, preparation was made to turn down a large bone flap in the right frontoparietal region. A preliminary temporal trephine with the patient under local anesthesia was done, and the dura was opened. A thin subdural membrane was found, but no blood. The opening in the temporal bone was enlarged and the dura opened widely for decompression. The subdural membrane separated easily from the dura and was detached over a wide area by traction. Exploration with a spatula beneath the temporal lobe did not reveal blood. The exposed cortex had a gray, translucent, wet appearance, with some clouding of the arachnoid, interpreted as a definite local arachnoiditis and edema of the brain. The wound was closed, leaving a subtemporal decompres-

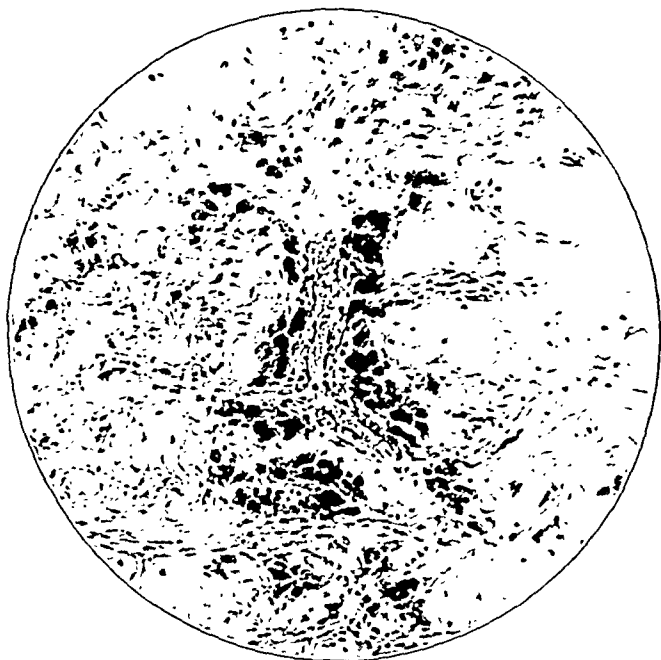


Fig. 3 (case 2).—Photomicrograph, low power, of the membrane of the subdural hematoma three and one half months after evacuation of the blood through a trephine.

sion. The former right frontal trephine was reopened and no subdural fluid was found, which confirmed the negative results of the needle puncture.

The patient made an uncomplicated recovery, and left the hospital on December 10. He was given 100 cc. of a 50 per cent solution of dextrose intravenously on the first postoperative day. There was moderate bulging over the decompression when he left, but this had entirely subsided when he was next seen, on Jan. 27, 1932. At this time he had no complaint, had gained in weight, strength and alertness, and felt entirely well. He has remained well.

Microscopic section of the subdural membrane (fig. 3) showed hyalinized connective tissue, a few thin-walled blood vessels and some hemosiderin pigment.

*Comment.*—This case illustrates the significance of anteroposterior displacement of the brain in the causation of chronic subdural hema-

toma, in that the sudden stopping of the car, with powerful bracing on the steering wheel, and no recognized injury of the head, gave rise to the condition. It also illustrates the successful evacuation of the hematoma by trephine and drainage, but with persistence of low grade pressure signs from residual local arachnoiditis and cerebral edema. This was relieved promptly by subtemporal decompression, which exposed the apparently insignificant loose remnant of the cyst wall seventy-one days after trephine drainage.

*CASE 3.—History.*—O. M. N., a man, aged 46, entered the Nebraska Methodist Hospital on April 23, 1923. He was referred by Dr. G. A. Young, with a diagnosis of chronic subdural hematoma. The patient entered the hospital with the complaint of headache, vomiting, inability to think and remember, and weakness. About Dec. 11, 1922, he fell from a load of hay and received a blow on his forehead, and a fracture of the left clavicle occurred. He was not unconscious, and drove his team to the barn. He had a headache following the accident, which soon disappeared, and he thought no more of the injury to the head. As soon as the clavicle had mended sufficiently, he resumed work and his health was normal. About Feb. 20, 1923, a sudden headache developed accompanied by vomiting, without nausea. The headache lasted a day or two; it was located indefinitely in the top of his head. He then appeared well again. During the following weeks, however, he had several similar attacks of headache lasting two or three days. During the two weeks preceding admission to the hospital his condition had become much worse and the headache more frequent and persistent; he had not been able to think clearly. During the past few days he had been very slow to respond; he appeared confused and at times unconscious.

*Examination.*—The patient lay in a semiconscious state. He responded very slowly and inaccurately. The left pupil was larger than the right; the fundus showed no elevation, and no other evident abnormality of the cranial nerves was present, although the patient's sluggish mental reaction prevented accurate tests of smell and taste. There was slight rigidity of the neck, and the Kernig sign was negative. Muscle power, reaction to pain, knee jerks and biceps tendon reaction appeared diminished on the left side. The Babinski reflex was negative. Spinal pressure on April 24 was 25 mm. of mercury; the fluid was clear and colorless, with 2 cells. The Wassermann reaction and the colloidal gold curve were negative. On April 25, the patient was more stuporous; the left abdominal reflex was absent, and the Babinski reflex and ankle clonus on the left were positive. The temperature and respiratory rate were normal; the pulse rate, from 50 to 60 a minute, and the blood pressure 95 systolic and 65 diastolic. Roentgenograms of the head were negative.

*First Operation.*—The findings suggested a tumor of the right frontal lobe. Examination of the fundus on April 25 showed an elevation of from 2 to 3 diopters in the left disk; the right disk was normal. The respiration had become Cheyne-Stokes in character; the pulse rate, 45, the stupor more profound. An intravenous injection of 200 cc. of buffered 15 per cent solution of sodium chloride was given and a right subtemporal decompression performed, with the patient under local anesthesia, as an emergency measure. There was no intracranial pressure during the operation, and no evident pathologic process was found in the right temporal region of the brain.

There was not much change following the operation, although consciousness was slightly improved. The left optic disk was normal on May 6. There was moderate bulging over the decompression, with little tension. On May 12, the mental condition was considerably improved, and absence of smell in the left nostril was observed. Replacement of ventricular fluid by 40 cc. of air was done through the decompression opening on May 12. The ventriculogram showed a markedly dilated right lateral ventricle with no deformity in the frontal region. The third ventricle also appeared markedly dilated and displaced to the right. No air was found in the left lateral ventricle. The interpretation was that there was a tumor in the left frontal region instead of the right as previously suspected. It was thought probably to be an inoperable glioma, owing to the rapid progression of symptoms, without marked intracranial pressure, and its location was thought to be the left frontal lobe. Chronic subdural hematoma was not thought of, although a history of injury of the head was obtained, because at that time this clinical condition was not well known.

*Second Operation and Course.*—A left frontal osteoplastic flap was turned down on May 17, with the patient under ethylene anesthesia. A large subdural hematoma was found over the left frontal lobe, filled with dark liquid blood and extending posteriorly as a thinner layer beyond the central fissure. The outer wall of the cyst was removed anteriorly, and a considerable amount of fibrinous clot was removed by sponging and irrigation. No attempt was made to remove the entire lining. The membrane was thin over the arachnoid, so that the flattened cerebral convolutions and fissures could be seen through it. A drain was placed in the cavity and another outside of the closed dura at the posterior angle of the wound.

There was considerable drainage of blood from the wound during the first twenty-four hours. The drains were removed on the second day, with no further evidence of bleeding. The wound healed without complications. There was moderate bulging over the right decompression for several days, which had subsided on May 24.

The patient made a rapid and uncomplicated recovery. He left the hospital on May 24, the seventh postoperative day, with continued nursing care at home. He resumed normal activity in a few weeks and continued to be well until Aug. 27, 1925, when he had three convulsions over a period of twenty-four hours. He reentered the hospital on August 28, and neurologic examination at that time gave entirely negative results. Examination of the spinal fluid showed: pressure, normal; cells, 2, and protein and sugar content, normal. He was dismissed on August 30, with a diagnosis of organic epilepsy, and medical treatment was advised. He has had occasional epileptic attacks since that time, mostly of the minor type, and on this account has some disability. His general health otherwise is good.

*Comment.*—This case illustrates the delay in diagnosis and treatment incident to imperfect knowledge of chronic subdural hematoma in 1923. Although a bone flap was turned down, the hematoma was treated essentially by evacuation and drainage. The desirability of a decompression during the period of recovery is shown by the bulging right temporal hernia which lasted several days. Recovery probably was hastened by the presence of this decompression. The appearance of epileptic attacks two years after the operation might indicate some residual scarring which could have been prevented by more radical

removal of the membrane. However, I should question whether less damage would be left by complete removal, which is not always possible or advisable.

*CASE 4.—History.*—C. N., a man, aged 57, entered the Nebraska Methodist Hospital on June 7, 1928. He was referred by Dr. C. E. Allenburger, with a diagnosis of chronic subdural hematoma.

The patient entered with the complaint of persistent right frontal headache, occasional vomiting, mental confusion and weakness. Early in April, 1928, while working in the field, he received an injury to the right side of his head. He wandered into the house about 11 a. m., apparently dazed and confused, with a severe lacerated wound in the right temporal region. The wound was sutured, and a roentgenogram was not taken. The mental confusion seemed to have disappeared by the evening of that day. He returned to work after a few days and seemed well, except for a gradually increasing right frontotemporal headache, which caused him to consult a physician on May 29. The following day he became quite weak, unable to walk, and entered a local hospital on June 2. Occasional vomiting began at this time. Mental confusion appeared on June 5, and he entered the Methodist Hospital on June 7.

*Examination.*—Examination showed mental dulness, difficulty in holding attention, a tendency toward jocularity, at times a mild stupor. The optic disks showed blurring of the margins and an elevation of 1 diopter; there was no defect in the visual fields, and all of the other cranial nerves were normal. There was a slight motor weakness in the left arm. The knee jerk was greater on the left than on the right; there were bilateral ankle clonus, a left plantar reflex and absence of abdominal and cremasteric reflexes. Otherwise the results of motor, sensory and coordination tests were normal, except for sluggish response. Roentgenograms of the skull were negative.

*Operation and Course.*—A preoperative diagnosis of chronic subdural hematoma in the right frontal area was made, and a right lateral, frontal trephine was done on July 8. A thin, partly organized old blood clot was found in the subdural space, but there was little free fluid. This wound was closed, and another trephine was done posteriorly in the right temple. An elevated line of bone in this region with quite adherent dura and obliterated middle meningeal artery suggested an old fracture and middle meningeal tear. The trephine opening was enlarged to 2 cm. in diameter, and the dura was opened crucially. At the inferior border of the opening a considerable quantity of clear fluid under pressure was released, apparently subarachnoid fluid, with the cortex visible in this region. A dark membrane covered the upper two thirds of the opening, and a trochar needle inserted into this released 2 or 3 ounces of dark brown fluid. The opening was enlarged, and a rubber tissue drain was inserted into this cavity. There was considerable drainage of blood-stained fluid during the first twenty-four hours, interpreted as partly cerebrospinal fluid. The drain was removed on the second day, with no further drainage.

The patient seemed more alert after the operation and had less headache. A spinal puncture on June 11 showed: pressure, 18 mm. of mercury; fluid, clear; cells, 8; protein, normal. He was rather restless for a few days and then became listless and drowsy. He was given active magnesium sulphate catharsis for the edema of the brain. Spinal puncture, on June 15, showed a low grade pressure, with normal fluid. A needle was inserted into the region of the hematoma on June 16, and only 8 cc. of brown fluid could be obtained, indicating satisfactory evacuation. The persistence of neurologic signs which preceded the operation, increasing stupor

with bilateral ankle clonus, and a suggestive spastic weakness of the right arm observed on June 29, suggested a bilateral hematoma. A left frontal trephine was done on June 30, and nothing was found, except an increase of subarachnoid fluid and prominence of the cortical blood vessels.

The stupor gradually increased to coma, with Cheyne-Stokes respiration, loss of pharyngeal reflexes and profuse sweating, with periods of slight remission. The pulse remained fairly good; the temperature ranged from 99 to 101 F. and the respiratory rate, from 20 to 30 a minute. On July 3, convulsive attacks developed, characterized by clonic spasm spreading from the right side of the face down the right side of the body, with conjugate deviation of the eyes to the right. These recurred for several days, and the patient's condition seemed very serious. The temperature rose to 103 F., the pulse rate, to 120, and the respiratory rate, to 40. He gradually improved, however, regained consciousness, became restless but more cooperative, and was able to be up in a chair on July 14. From this time he improved rapidly. He left the hospital July 20. He gradually recovered strength, and when seen on Sept. 11, 1928, appeared to be entirely well. He was seen again on Oct. 30, 1930, and reported ability to do a full day's work on the farm as well as before his injury.

*Comment.*—This case presents several puzzling features. The operative findings indicated a right middle meningeal injury, but the location of the hematoma was almost too far medial and the symptoms too slow in developing for its source to be this vessel. The persistence and increase of symptoms after drainage of the hematoma led to exploration of the left side, with negative results. Postoperative edema of the brain did not seem to explain the profound depression without pressure; cortical degeneration seemed necessary; but the patient's complete recovery would negate this theory. Perhaps a bone flap or larger decompression should have been done, since there was evidence of organization of the clot in the frontal region. I doubt, however, if he would have survived this major operation. Intravenous injections of a hypertonic solution of dextrose might have been given to advantage, although the excess of subarachnoid fluid on the left side indicated adequate dehydration by magnesium sulphate. It is possible that the patient was too much dehydrated, and that hypotonic rather than hypertonic fluids were indicated.

*CASE 5.—History.*—P. M. S., a man, aged 71, entered the Immanuel Hospital on Feb. 11, 1932. He was referred by Dr. H. A. Blackstone, with a diagnosis of chronic subdural hematoma.

The patient fell on a slippery street on Dec. 11, 1931, striking the right fronto-temporal region of his head. He got up immediately after the injury and went home alone, with no symptoms except a "black eye." About two weeks later, his son noted that his left knee seemed stiff, and that he dragged the left toes in walking. The left arm became weak about two weeks later, and the weakness gradually increased to disabling left hemiplegia. He had no headache and did not vomit, and no mental disturbances appeared until Feb. 1, 1932, when he had influenza and became increasingly drowsy, with stupor and incontinence two weeks later.



*Examination.*—Neurologic examination, on February 16, showed: left hemiplegia of the central type; absence of the left abdominal and cremasteric reflexes; normal fundi; spinal pressure, 10 mm. of mercury; fluid, clear with a very faint yellow tint; cell count, 2; protein, 13 mg. per hundred cubic centimeters; colloidal gold curve, negative. The pulse ranged between 64 and 84; the blood pressure was 120 systolic and 80 diastolic. He was stuporous and slept with obstructed breathing.

Owing to his age and lack of intracranial pressure, a diagnosis of right lateral cerebral thrombosis was favored, although the traumatic history suggested chronic subdural hematoma. In a report on the roentgen findings, Dr. Tyler stated that there was "an area of increased density in the right lateral frontal region very suggestive of hemorrhage between the cranial vault and the brain, pushing the latter away from the skull." Definite improvement following the intravenous injection of 100 cc. of a 50 per cent solution of dextrose favored the diagnosis of chronic subdural hematoma.

*Operation and Course.*—An exploratory trephine in the right lateral frontal region was done on February 20, and a typical dark subdural membrane was encountered. Incision through this released an ounce or more of dark brownish liquid blood. After evacuation the blood cavity was found to extend several centimeters medially and into the temporal region. There appeared to be an inner chamber of blood which required separate opening before the pale fairly normal-appearing flattened cortex could be seen. A considerable portion of the cyst membrane was removed by dissection and traction. The wound was closed, and a small rubber tissue drain was left in place for forty-eight hours.

Following the operation there was prompt improvement in mental reaction and the disappearance of drowsiness, but there was little improvement in the paralysis. This, however, gradually improved over a period of a few months, and at the present writing the patient has resumed normal activity, with slight disability.

*Comment.*—This case illustrates the danger of a mistaken diagnosis of cerebral vascular disease on account of the age of the patient. The noteworthy roentgenographic report of a subdural shadow and the improvement following injection of a hypertonic solution of dextrose, with a history of trauma, led to the correct diagnosis. In this case recovery after simple trephine drainage was complete but slow. It is possible that more rapid recovery would have occurred if a larger opening had been made or a decompression done. However, the age and poor condition of the patient seemed to contraindicate a more radical surgical procedure. His ultimate recovery was satisfactory.

# OSTEOCHONDRITIS OF THE HEAD OF THE FEMUR

## AN EXPERIMENTAL STUDY

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The exact etiology of osteochondritis of the head of the femur<sup>1</sup> is still undetermined. Various theories of the cause of this disease have been advanced, the most reasonable of which may be considered under the headings of infection, trauma, embolism and maldevelopment.

The evidence in favor of infection as the etiologic agent is based on a few bacteriologic studies. Legg<sup>2</sup> scraped tissue from a large area of rarefaction in the neck of the femur of a patient suffering from this disease and found that staphylococci grew in cultures from the material so obtained. Kidner<sup>3</sup> obtained staphylococci from the granulation tissue found in necrotic areas in the metaphyseal region of the upper end of the femur in a similar case. McWhorter<sup>4</sup> likewise found the staphylococcus in a single case. Phemister<sup>5</sup> removed part of the upper femoral epiphysis after curetting the interior, and obtained no microbic growth (1921), but in a later study (1930) of two cases, he found in one streptococci in cultures of tissue removed at operation. In this case, the wound healed by primary intention, but a low grade febrile reaction persisted for two weeks. A blood culture taken during this period yielded the same organisms as those which were recovered from the bone. The histologic picture was that of necrosis of the bone accompanied by marked fibrosis and phagocytic reaction of the fixed tissues.

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1. Synonyms for osteochondritis of the head of the femur are Legg-Calvé-Perthes' disease, osteochondritis deformans juvenilis coxa and pseudocoxalgia.

2. Legg, A. T.: An Obscure Affection of the Hip Joint, *Boston M. & S. J.* **62**:202 (Feb. 17) 1910.

3. Kidner, F. C.: Perthes' Disease, *Am. J. Orthop. Surg.* **14**:339, 1916.

4. McWhorter, G. L.: Operation on the Neck of the Femur Following Acute Symptoms in a Case of Osteochondritis Deformans Juvenilis Coxae, *Surg., Gynec. & Obst.* **38**:632, 1924.

5. Phemister, D. B.: Operation for Epiphysitis of the Head of the Femur (Perthes' Disease), *Arch. Surg.* **2**:221 (March) 1921; Silent Foci of Localized Osteomyelitis, *J. A. M. A.* **82**:1311 (April 26) 1924. Phemister, D. B.; Brunswick, A., and Day, L.: Streptococcal Infections of the Epiphyses and Short Bones, *J. A. M. A.* **95**:995 (Oct. 4) 1930.

However, in a number of patients subjected to exploratory operation by other workers, the cultures failed to show bacterial growth.

As a definite history of trauma is often obtained in osteochondritis it is difficult to discount this factor entirely. Not infrequently changes simulating osteochondritis develop after closed manipulation in congenital dislocation of the hip. It has been suggested that such trauma may injure the vessels supplying the femoral epiphysis and that the circulatory disturbance produced thereby may cause atrophy of the bone with collapse of the head. In this connection it may be well to recall that the head of the femur receives its main blood supply from the vessels of that portion of the capsule which is reflected upward along the neck to the chondro-osseous margins. A rich anastomosis of these vessels encircles the entire neck of the femur with the largest vessels situated posteriorly and superiorly. In young persons the ligamentum teres contains blood vessels which aid in the nutrition of the head. Leriche and Policard<sup>6</sup> suggested an explanation of osteochondritis on the basis of traumatic vasomotor changes. They found that rarefaction of bone is the result of increased circulation. Bentzon,<sup>7</sup> whose investigations support this idea, believes that the arteries which supply the femoral head are so arranged that they are exposed to mild lesions of pressure and stretching, especially in young persons in whom trauma may cause a bending of the cartilaginous part of the epiphysis without producing a real epiphyseolysis. He stated that since the arteries are exposed to moderate traumatisms, it is possible that the vasomotor nerves in the adventitia may be damaged in such a way that they become blocked, with the result that an active hyperemia of the epiphyseal body occurs. By injections of alcohol around the arteries of the upper epiphysis of the femur in young rabbits he produced coxa plana in several instances, and histologic examination of the femoral heads showed a picture quite characteristic of that condition.

Axhausen<sup>8</sup> suggested that Legg-Calvé-Perthes' disease, Kienbock's disease, Köhler's disease and similar lesions might represent the results of a vascular occlusion caused by an embolus of tubercle bacilli or pyogenic organisms. He believes that bacteria may lodge in one or more of the smaller vessels, where they are destroyed by the local protective

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6. Leriche, R., and Policard, A.: *Normal and Pathological Physiology of Bones*, St. Louis, C. V. Mosby Company, 1928, p. 214.

7. Bentzon, P. G. K.: A New Theory About the Pathogenesis of Coxa Plana and Other Manifestations of "Local Dyschondroplasia," *Brit. J. Radiol.* **31**:439, 1926.

8. Axhausen, G.: Nicht Malacie, sondern Nekrose des Os Lunatum Carpi, *Arch. f. klin. Chir.* **129**:26, 1924; Ueber anämische Infarkte am Knochensystem und ihre Bedeutung für die Lehre von den primären Epiphyseonekrosen, *ibid.* **151**:72, 1928.

forces with a sterile embolic necrosis as the end-result. In support of this contention it can be stated that tubercle bacilli have been found in several cases which have shown a clinical course similar to that of Legg-Calvé-Perthes' disease.

Calot<sup>9</sup> and Mürk Jansen<sup>10</sup> offer to explain the disease on the basis of developmental anomalies. The former believes that osteochondritis of the femoral head is a condition of arrested development of the hip joint, with a tendency to congenital subluxation or dislocation. An imperfect contact of the head in the acetabulum brings about a condition of mechanical instability which results in flattening and irregularity of the head. Mürk Jansen stated that in these cases the acetabula are abnormally flat (*ischium varum*), and the head changes its shape gradually because of the deranged mechanical conditions.

Because of the limited amount of material available for microscopic examination, the histopathology of osteochondritis of the head of the femur has not been investigated thoroughly. Nevertheless, the essential features of the anatomic changes have been well described in a few pathologic studies made by German workers (Perthes, Axhausen, Riedel, Heitzmann, Konjetzney, Brandt and Klages). The earliest and most striking change consists in necrosis of the bony trabeculae of the femoral head and of the bone marrow, resulting occasionally, when extensive, in compression fracture of the head. This necrosis is followed immediately by regenerative activities on the part of the fibroblasts. Beginning as a zone of granulation tissue surrounding the necrotic area, the fibrous tissue tends to reorganize the areas of necrosis. Subsequently, there is not only diffuse fibrosis of the bone marrow, but also formation of new bone and cartilage as the result of the metaplasia of the fibroblasts or the increased activities of the chondroblasts and osteoblasts. In the granulation tissue degenerative changes may develop. These consist especially of hemorrhage, edema and finally the formation of small cysts. Additional changes also occur at the epiphyseal line and in the joint cartilage. The epiphyseal line may be broken into irregular islands of cartilage, with the result that the vascular channels between the medullary bone of the head and neck become anastomosed. The hyaline matrix of the joint cartilage may become edematous or fibrillar, and the cartilage cells may either absorb stain poorly or appear greatly shrunken and atrophied.

That one or more of the causal factors previously suggested plays a part in the etiology of osteochondritis of the hip seems possible. It is

9. Calot, F., and Collen, H.: *L'ostéochondrite de la hanche*, Presse méd. **30**: 35 (Jan. 14) 1922.

10. Jansen, Mürk: *Flattened Hip Socket and Its Sequelae*, J. Bone & Joint Surg. **5**:528, 1923.

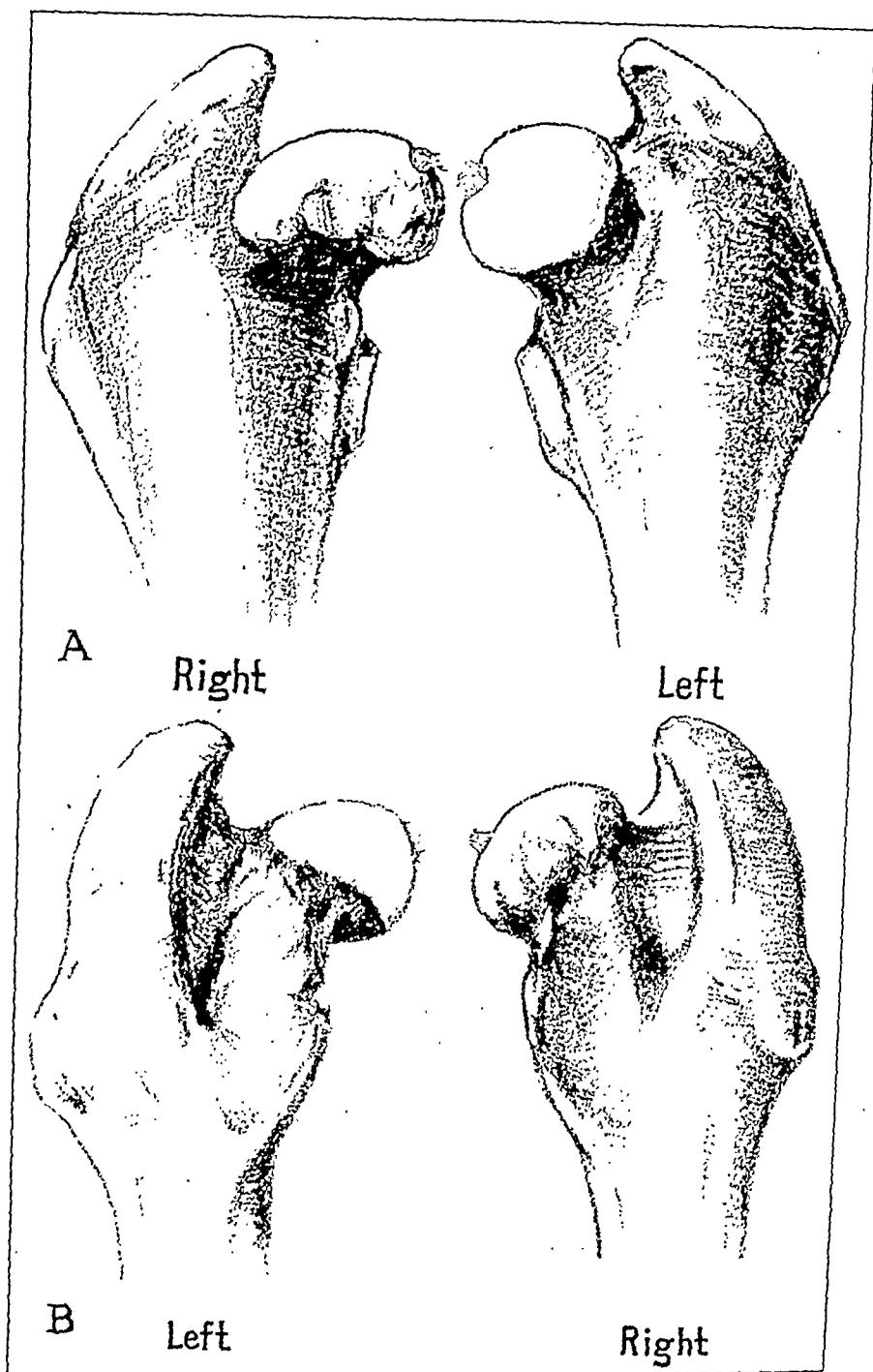


Fig. 1.—*A*, drawings (anterior view in case 365) showing the early roughening and flattening of the right femoral head. The operation, which was performed three months previously, included ligation of the round ligament along with stripping of the periosteum from the neck. Note that most of the changes of the head are in the portion nearest the epiphyseal cartilage plate. The normal left femoral head is shown for comparison. *B*, posterior view of the same specimens.

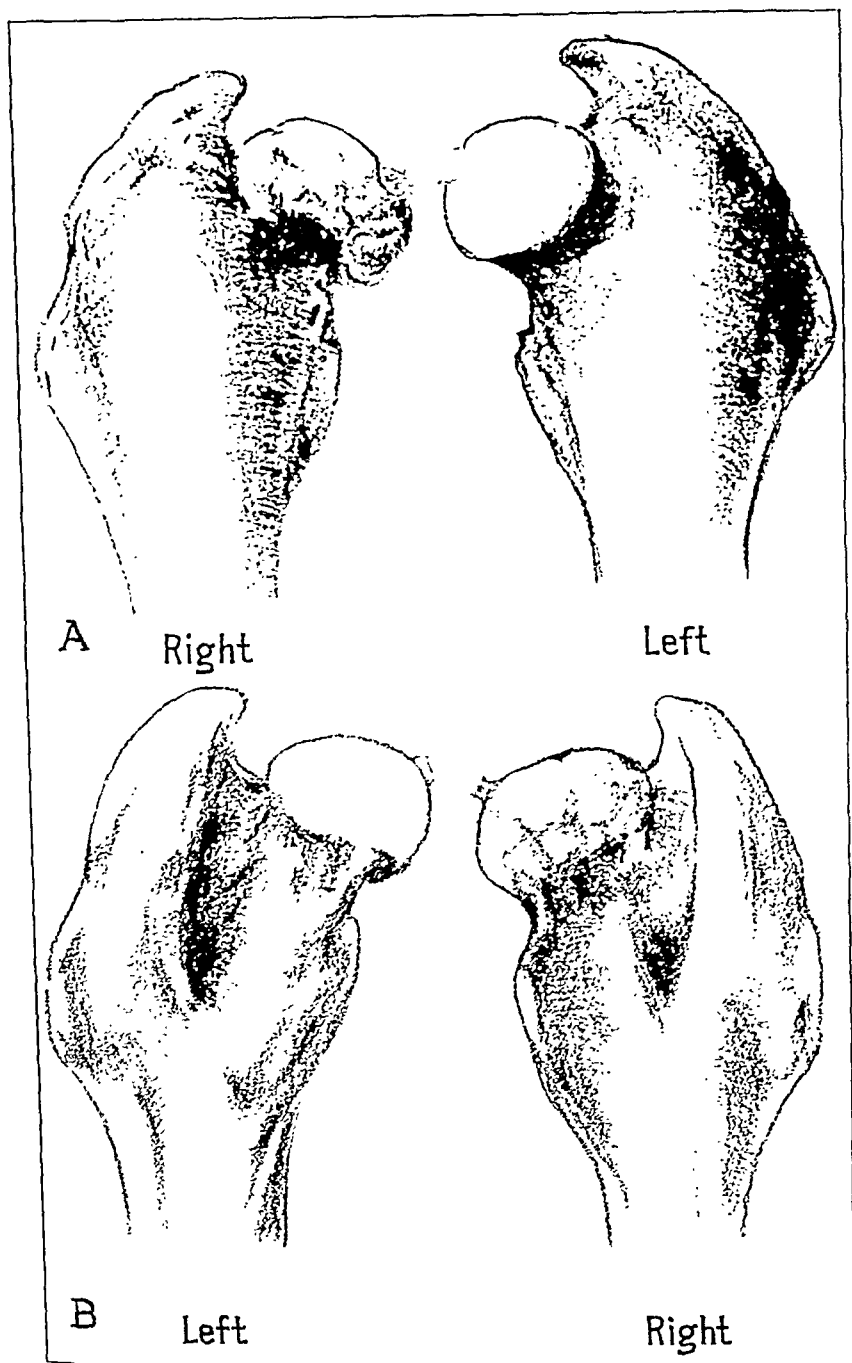


Fig. 2.—*A*, drawing of the autopsy specimen in case 399 removed four months after ligation of the round ligament and stripping of the periosteum from the neck (right side). Note that the changes are more advanced than those in figure 1, and include roughening and flattening of the entire head. The normal left femoral head is shown for comparison. *B*, posterior views of the same specimens.

certain that there are many borderline cases which simulate closely the changes following a low grade osteomyelitis. There is a great deal of clinical evidence in support of the traumatic theory. After an extensive survey of the literature, it seemed to us that the cause of the disease



Fig. 3.—*A*, photomicrograph of the femoral head of dog 16, two and one-half months after ligation of the round ligament and stripping of the periosteum from the neck. Almost all of the cancellous bone of the head is necrotic. Reduced from  $\times 12$ . *B*, photomicrograph of a small area of section shown in *A*. Note the necrosis of the medullary bone and the normal cartilage of the epiphyseal plate. Reduced from  $\times 100$ .

might lie in some deficiency in the vascular supply of the head of the femur, and consequently this study was undertaken. In a series of

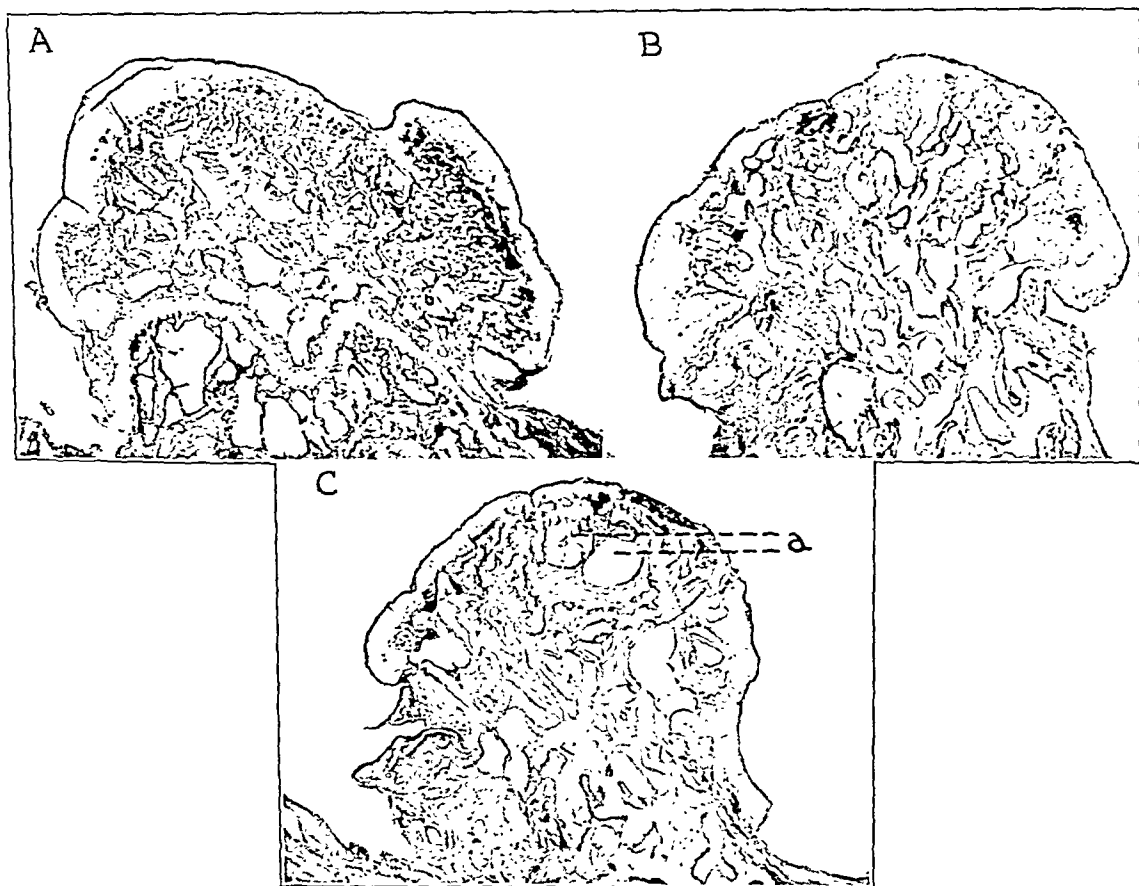


Fig. 4.—*A*, photomicrograph of the femoral head of rabbit 384, three months after ligation of the round ligament and stripping of the periosteum from the neck. The head appears flattened and its surface is irregular as the result of necrosis and atrophy of the underlying cancellous bone. Note the thinning out of the articular cartilage. The large cystlike spaces on either side of the epiphyseal cartilage are artefacts. Reduced from  $\times 20$ . *B*, photomicrograph of the femoral head of rabbit 367 four months after operation. Note the marked loss of cartilage on the articular surface. The epiphyseal cartilage has disappeared except for a small portion at the left margin, and the bone of the head is in the process of replacement. The cystlike spaces are artefacts. Reduced from  $\times 22$ . *C*, photomicrograph of the femoral head of rabbit 358 four and one-half months after the same operation as in *A*. Note that the head appears slightly flattened. In certain places the articular cartilage is thin and irregular while in others it is absent. The lateral margins of the articular cartilage overhang the bone of the neck. There are two well defined cysts (*A*) near the articular surface. The other cystlike spaces are artefacts. Reduced from  $\times 18$ .



experiments on animals, attempts were made to bring about a deficiency of the circulation of the head of the femur, to determine microscopically the changes in the head of the femur after varying periods of time and to see if the resultant changes simulated in any way the clinical syndrome termed Legg-Calvé-Perthes' disease.

#### METHOD

Five dogs and twelve rabbits were used. The ages of the dogs varied from 2 to 4 months and the ages of the rabbits from 2 to 3 months. Young animals

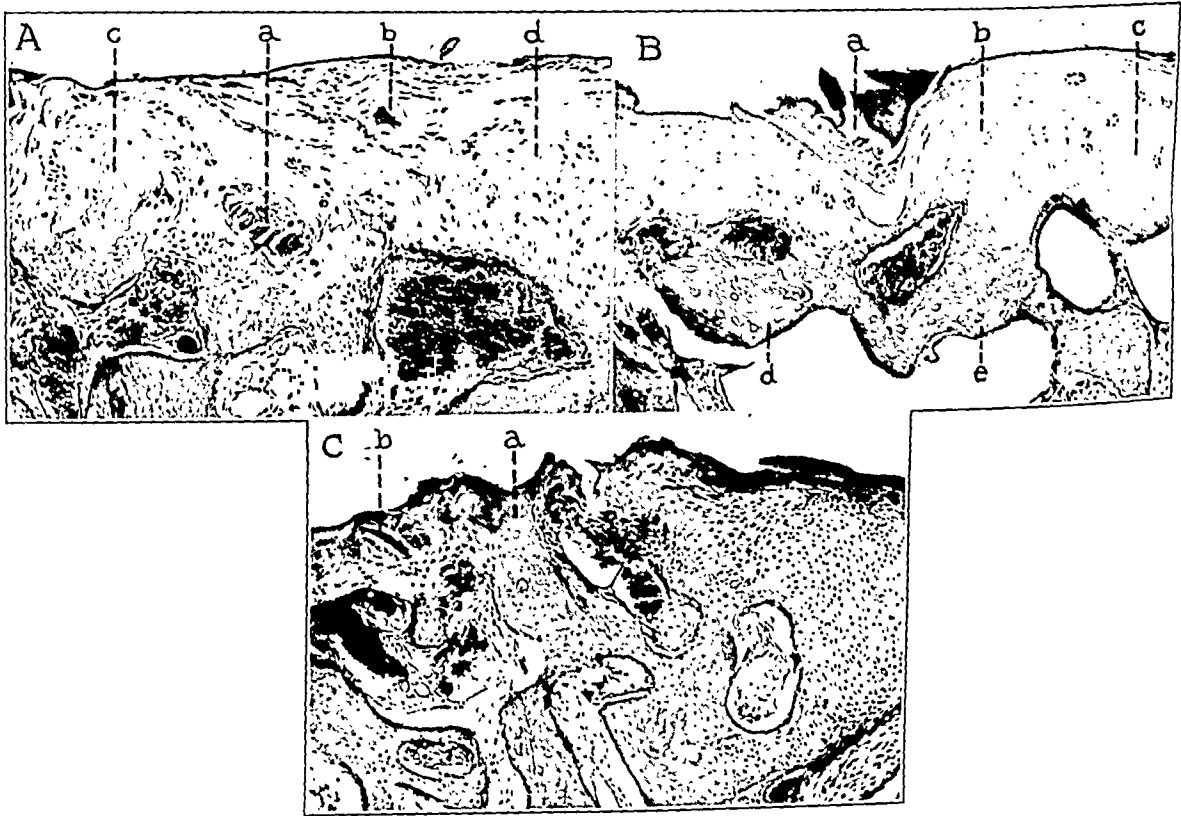


Fig. 5.—*A*, photomicrograph of a portion of the articular cartilage from figure 4 *B*, showing areas of necrosis (*a* and *b*) within the substance of the cartilage and necrotic cartilage cells (*c* and *d*). Reduced from  $\times 120$ . *B*, photomicrograph of another portion of the articular cartilage shown in figure 4 *B*, revealing a more advanced stage of necrosis. The indentation (*a*) contains a piece of necrotic cartilage. Note the degenerated cartilage cells at *b* and *c* and the degenerated bone cells at *d* and *e*. Reduced from  $\times 135$ . *C*, photomicrograph of a third portion of the articular cartilage shown in figure 4 *B*, showing a small area in which the articular cartilage has disappeared, with the result that the bone (*a*) is on a level with the cartilage of the surface. The bone cells near the articular surface are necrotic. There is another spicule of dead bone at *b*. Reduced from  $\times 120$ .

were chosen so that the epiphyses might show active growth of bone and cartilage. Inhalation ether anesthesia was employed in all cases. With aseptic technic the

hip joints were opened through an anterior superior incision. The blood vessels of the femoral head were interrupted according to one of the several methods to be described later, and the incisions were closed with fine silk sutures. Special attention was given to the reapproximation of the subcutaneous tissues and skin, and the wounds were sealed with collodion dressings. Animals in which infection of the hip joint developed were discarded. Roentgenograms were made following the operation and at the time of the autopsy. The animals were killed by electrocution, and autopsies were performed at periods of time varying from two weeks to four and one-half months after the operation. Cultures were taken from the hip joints

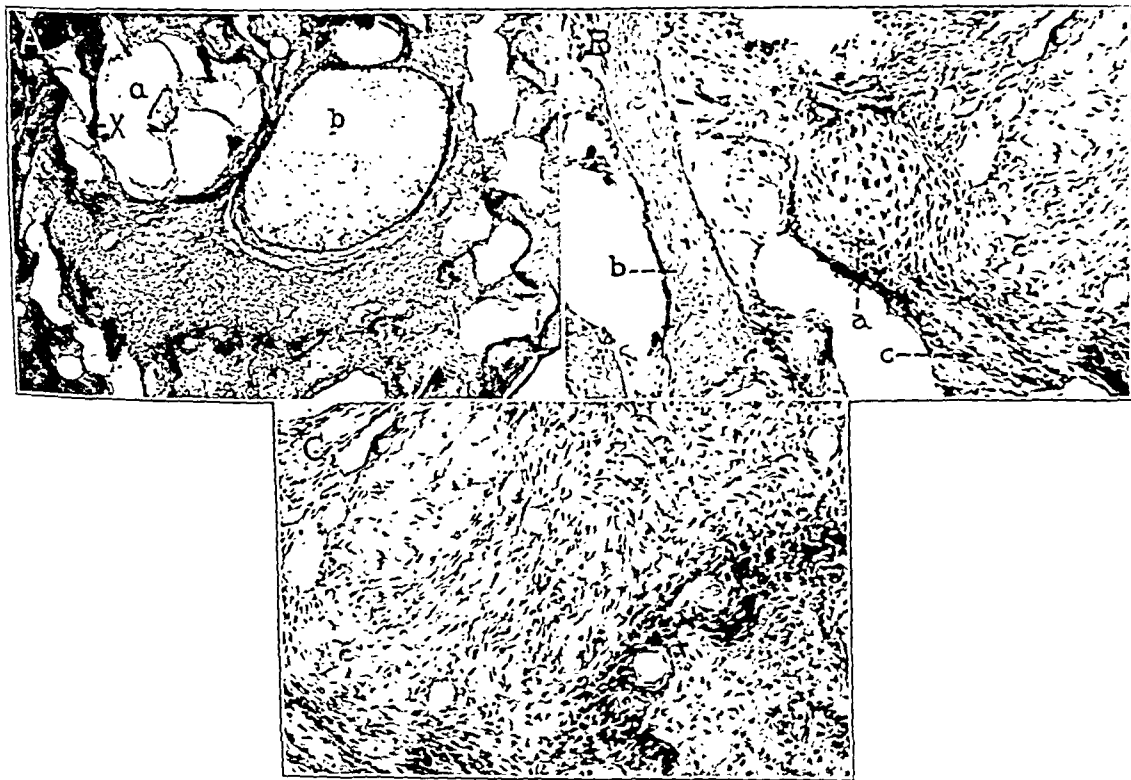


Fig. 6.—*A*, photomicrograph of the two cystic areas shown in figure 4 *C*. Cyst *a* contains a bone trabecula, part of which is necrotic (*X*). This cyst appears to be younger than cyst *b*, which is surrounded by fibrous tissue. Note the metaplasia of fibrous tissue with the formation of cartilage and new bone. *B*, photomicrograph showing a nest of young cartilage cells (*a*) of *A*. Note the spicule of old bone (*b*) to the left, and the spicule of new bone (*c*) next to the cartilage. Reduced from  $\times 155$ . *C*, photomicrograph of an area from *A*, showing new bone in the lower right corner. Note the vascular fibroblastic tissue which surrounds the new bone. Reduced from  $\times 150$ .

which were operated on, and the upper ends of both femurs (the normal hip and the one operated on) were removed for gross and microscopic examination.

Three groups of experiments were performed. A description of a typical experiment in each group is given.

GROUP A.—*Alcohol injected into the periosteum of the neck of the femur.*

Dog 4 was 2 months of age. The right hip joint was opened through an antero-superior incision. The capsule was incised transversely and, through a very fine hypodermic needle, several minims of a solution of 95 per cent alcohol was injected into the periosteum of the neck of the femur and into the overlying synovial membrane. The capsule of the joint was not resutured. The muscles and other soft tissues were closed by sutures of fine silk, and the wound was sealed with collodion. The hip joint was not immobilized. Roentgenograms of both hips were taken shortly after the operation and at the time of the autopsy. The animal was killed two months after the operation, cultures were taken from the hip joint and microscopic sections of both femoral heads were made. Similar experiments were done on dogs 3 and 5 except that in these two animals the condition was allowed to progress further, that is, for three and four months.

GROUP B.—*Alcohol injected into the periosteum of the femoral neck; periosteum also stripped back from the epiphyseal line to the base of the neck of the femur.*

Rabbit 334 was 2 months old. The right hip joint was exposed and the capsule incised transversely. A solution of 95 per cent alcohol was injected into the periosteum and synovia which surrounded the neck of the femur. A fine knife and a small blunt dissector were used to strip the soft tissues from the head back to the base of the neck. Closure of the wound was made by means of interrupted fine silk sutures. Roentgenograms were taken immediately after the operation and again at the time of the autopsy, two weeks later. Cultures were taken from the synovial fluid and from the tissue fluids of the synovial membrane. At this time the upper ends of both femurs were removed for gross and microscopic examination. Three other experiments of the same type were performed on rabbits 218, 358 and 396, the first animal being killed after two and one-half months and the other two after four months.

GROUP C.—*Round ligament ligated with silk suture; periosteum stripped from the neck; silk ligature placed around the neck.*

Rabbit 384 was 2½ months old. The femoral head was exposed as in the previous experiments. By pulling the great trochanter laterally the round ligament was stretched enough to allow the head of the femur to be subluxated. By means of a small curved suture carrier a heavy silk ligature was made to encircle the round ligament and was tied around that structure. Then a circular incision was made through the periosteum at the junction of the head and neck, and the periosteum along with the reflected portion of the synovial membrane was stripped back to the base of the neck of the femur. A silk ligature was placed around the neck to insure the interruption of all of the blood vessels in the periosteum. The wound was closed in the usual manner. Roentgenograms were taken after the operation and again at autopsy, three and one-half months later. At the autopsy, cultures were taken from the hip joint, and the upper ends of both femurs (the normal hip and the one operated on) were removed for gross and microscopic examination. Ten similar experiments were performed on animals 16, 225, 335, 338, 384, 365, 367, 399, 26 and 358. The first four were killed after two and one-half months, the next two after three months, the next two after four months and the last two after four and one-half months.

## RESULTS

GROUP A.—In the three dogs comprising this group there were no disturbances in the growth of the head or neck of the femur. Examina-

tion of the gross specimens showed a moderate amount of fibrosis and thickening of the synovial membrane. The anterior portion of the joint capsule was adherent to the periosteum of the neck. The histologic pictures of the femoral heads showed nothing of importance. There was some thickening and fibrosis of the periosteum of the neck at the sites where the injections of alcohol had been made.

GROUP B.—There was no gross evidence of disturbance of growth in any of the cases in this group. In the first case the autopsy was performed two weeks after operation, and the sections showed that vascular fibrous tissue and periosteum had already grown across the surface of the neck which had previously been denuded. In the other three cases microscopic examination of the joint cartilage showed areas in which the cartilage cells were crowded together and had lost their orderly arrangement. The crowding of cells appeared to be due to the loss of matrix. In a few places, the matrix showed swelling and fibrillation. A few cartilage cells stained poorly, showing a marked contrast to the deeply stained cells in their immediate neighborhood. The bone trabeculae showed a few small areas in which the cells were necrotic, but otherwise there was no change. The bone marrow appeared fatty and contained only small numbers of myeloid cells. The epiphyseal cartilage plates were not abnormal. Except for a moderate increase in the fibrous tissue of the periosteum nothing unusual was observed in the microscopic sections of the femoral necks.

GROUP C.—In the nine cases of this group the round ligament was ligated with a silk suture and the periosteum stripped back from the head to the base of the neck. In addition, to insure obstruction of all of the periosteal blood vessels, a silk ligature was tied about the neck. In every case except one, examination of the gross specimens revealed evidence of disturbance of the growth of the head. The round ligaments were smaller than normal and apparently fibrosed. In six of the cases the head appeared flattened and in places the cartilaginous surfaces were roughened and depressed. In the other three cases the cartilaginous surfaces appeared regular in outline, but apparently were thinned in places. In two of the latter cases, there also was gross evidence of early osteoarthritic roughening of the bone at the margins of the head of the femur.

The microscopic observations in all cases of group C were similar, and a résumé of these changes in a typical case is given: The cartilage of the head showed an irregular surface and a lack of uniformity in thickness (fig. 4 *A*, *B* and *C*). The average thickness was about two thirds of the normal. In a few places, the cartilage was absent, leaving the underlying bone exposed (figs. 4 *B* and 5 *C*). There were numerous foci in which the nuclei of the cartilage cells were stained only

faintly with eosin or not stained at all (fig. 5 *A* and *B*). Such unstained nuclei undoubtedly indicated death of cells. The cartilage matrix showed marked variation in its stain, having normal areas of light blue intermingled with areas of red. Fragments of red-stained tissue debris, apparently derived from cartilage matrix, were found on the surface of the cartilage, as well as in its substance (fig. 5 *A* and *B*). Many of the bony trabeculae of the head were irregular in size and smaller than normal. In places these trabeculae were absent, having been replaced by fibrous tissue or cysts (fig. 4 *C*). In many places, especially beneath the cartilaginous surface of the head, the bone cells were either partly or completely degenerated (fig. 5 *B* and *C*). In a few areas, not only were the bone cells necrotic, but the bone matrix had assumed a granular crumbly appearance with roughened edges (fig. 6 *A*). The bone marrow was fibrosed more than normal. In one section (fig. 6 *A*) there were two large cysts, one of which was in an early stage of formation and had an irregular bit of necrotic bone in the center and another bit at the edge. There was a slight degree of fibrosis along the wall. The other cyst was well lined by a thick layer of fibrous tissue which was partly hyalinized and, in part, very cellular. In one portion of the cellular area could be seen transformation of the fibroblast-like cells into typical new bone and, in another portion, into typical hyaline cartilage (fig. 6 *A*, *B* and *C*). The bone marrow of the neck was largely fatty, being in marked contradistinction to that of the normal femur which was more cellular. The cultures which were taken from the hip joints did not show any evidence of bacterial growth.

#### COMMENT

In the experiments under group A attempts were made to produce osteochondritis by the method of Bentzon, that is, by the injection of alcohol into the periosteum of the neck of the femur. No important changes were observed. The bone and cartilage remained normal, and there was no flattening or fragmentation of the head. The epiphyseal cartilages and the femoral necks were in no way different from those of the control hips of the opposite side.

In the cases of group B, the periosteum and the reflected portion of the synovial membrane was stripped from the chondro-osseous margins of the head to the base of the neck. Alcohol was injected into the periosteum in order to increase the amount of fibrosis and to delay the formation of a new vascular supply. Microscopic sections of those cases showed nothing of importance except for a few very small areas of aseptic necrosis of bone. Apparently the circulatory embarrassment was sufficient to cause only a limited amount of necrosis, which was reparable without gross changes in the head.

In the last group of experiments (group C), the periosteum was stripped from the neck as in the preceding cases, and in addition the round ligament was tied with a silk suture. Since the epiphyseal cartilage plates were intact there followed, necessarily, a severe interruption of the blood supply to the femoral head. In the first experiment of group B, it was seen that new blood vessels had bridged the gap in the periosteum after two weeks. Therefore, in the experiments in group C, it was believed that the circulatory deficiency of the head lasted for only the short period between the time of operative interference and the time when the collateral supply became effective.

The results of the circulatory disturbances were quite constant in all of the cases in the last series. In all of the animals except one, gross examination revealed roughening and slight flattening of the head. In this exception (dog 16, fig. 3 *A* and *B*) gross examination showed nothing particularly abnormal; there was no deformity of the head, and the articular cartilage was smooth and of almost uniform thickness. Microscopic examination, however, showed that practically all of the bone cells of the head were necrotic and that the bone marrow, which consisted largely of fatty tissue, also was necrotic. These changes were interpreted as the early stages of massive aseptic necrosis. We believe that flattening and fragmentation would have followed, provided the condition had been allowed to progress for a longer period of time.

Microscopic examination of the other cases in group C showed uniform pathologic changes. The characteristic changes in the head were patchy, aseptic necrosis of the bone, accompanied by a few areas of necrosis of the articular cartilage. Active repair of bone and cartilage was seen bordering on the areas of necrosis. As the result of weight-bearing on the affected bone, the heads showed gross roughening and flattening of the articular surfaces. Of particular interest were the well defined cystic spaces which were found in the marrow cavities. Apparently these cystic spaces represented areas of degeneration of medullary bone or of the marrow tissues.

#### CONCLUSIONS

Vascular disturbances of the head of the femur were produced in animals by ligation of the round ligament and by stripping the periosteum from the neck of the femur.

Several months following these procedures the femoral heads showed gross and microscopic changes which were similar to those found in the human disease known as Legg-Calvé-Perthes' disease or osteochondritis of the head of the femur.

# PERIARTERIAL SYMPATHECTOMY IN FRACTURES

AN EXPERIMENTAL STUDY

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One of the essential factors in the healing of any fracture is a good and free supply of blood. This was first emphasized by Hilgeneiner,<sup>1</sup> Bier<sup>1</sup> and others, who advised the institution of measures to promote passive hyperemia in an effort to increase the variable phenomena usually present in all fractures. Leriche<sup>2</sup> has shown that following any injury, a reflex vasoconstriction occurs which is soon followed by vasodilatation about the area of the initial trauma. If, however, a periarterial neurectomy or a ganglionectomy is performed, the primary contraction of the involved vessels is followed within a few hours by a vasodilatation of the arterial tree and a marked increase in the blood volume. If these procedures produce an active hyperemia, they should then have a field of usefulness in the treatment of certain groups and types of fractures. Much experimental work has been recorded in recent years dealing with the effect of ganglionectomy and periarterial neurectomy on the healing of fractures.

Palma<sup>3</sup> performed a series of experiments on twelve adult rabbits from 12 to 18 months old. Both radii were fractured, and the lower cervical sympathetic ganglion was removed on one side. The results in the control series and in that in which the fractures were treated by means of ganglionectomy were widely different. Both roentgen and histologic examinations indicated an acceleration of the normal processes of repair on the side subjected to ganglionectomy. Marked connective tissue proliferation was observed five days after the fracture, whereas the control side showed little or none. The transformation of the callus from fibrous tissue into cartilage was almost completed by the tenth day, whereas it scarcely appeared on the control side. Some small

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1. Cited by Uffreduzzi, O.: *Arch. ed atti d. Soc. ital. di chir.* **31**:1, 1924.

2. Leriche, R.: *Ann. Surg.* **88**:449 (Sept.) 1928.

3. Palma, R.: *Ann. ital. di chir.* **4**:85, 1925.

zones of adult bone tissue could be distinguished on the sympathectomized side within fifteen days, while the callus on the control side was merely cartilaginous. Twenty days from the date of fracture, the cartilage on the experimental side had completely changed into bone, whereas on the control side there were small islands of bone instead, and the callus was still mainly cartilaginous. The resorption of callus on the experimental side was well advanced by the thirtieth day, whereas it had hardly started on the control side. The process of ossification on the sympathectomized side was practically completed by the forty-fifth day; that on the control side was one stage less advanced, owing to the presence of bridges and islands of bone in the medullary callus which had not as yet been absorbed. Palma concluded that ganglionectomy accelerated the process of callus formation and transformation about the fracture by inducing a greater blood supply in the entire vascular territory involved.

Uno<sup>4</sup> excised the abdominal sympathetics between the second lumbar and the second sacral vertebra on the right side and fractured both fibulae. Callus formation and healing of fractures were more marked on the ganglionectomized side. Eleven of twelve cases showed definite evidence of the formation of new vessels and a dilatation of the vascular tree with a marked hyperemia. When the fractures of ganglionectomized animals were compared with a series in which periarterial sympathectomy had been performed, the bony union was found to be more marked in the former.

Horton and Craig<sup>5</sup> noted a definite increase in vascularity in the arterial tree of the lower extremity in which the sympathetic innervation had been interrupted by unilateral sympathectomy, ganglionectomy and ramisectomy. This change was not apparent in an experimental animal in which a periarterial sympathectomy neurectomy was performed on the left femoral artery for 5 cm. The stereoscopic x-ray films made six days later on the dead animal were produced by injecting the arterial tree with mercury under its own weight.

Uffreduzzi<sup>6</sup> conducted a series of experiments on young rabbits. He produced bilateral symmetrical fractures of the ulna, and performed a periarterial sympathectomy for about 2 cm. of the axillary and upper portion of the humeral arteries. Roentgen and histologic observations of the processes of repair were made on the sixth, twelfth, twentieth, thirtieth, fortieth and fiftieth days.

It was noted on the twelfth day that the callus on the sympathectomized side was more abundantly vascularized. By the twentieth day,

4. Uno: *Arch. f. jap. Chir.* **3**:106, 1926.

5. Horton, B. T., and Craig, W. M.: *Proc. Staff Meet., Mayo Clin.* **4**:240 (Aug. 7) 1929.

6. Uffreduzzi, O.: *Arch. ed atti d. Soc. ital. di chir.* **31**:1, 1924.



the ossification of the fibrocartilaginous tissue and the callus was noticeably far advanced, and by the thirtieth day, no traces of cartilage were visible. Roentgenograms of the sympathectomized side taken on the fifteenth day showed visible callus which was not apparent on the control side. This callus had increased in size on the twentieth day. Both roentgen and histologic examinations made on the forty-fifth and fiftieth days showed that ossification was taking place. The fusion of the newly formed bone with the fragments took place first on the side that had been sympathectomized, and, in addition, the ossification of the young bone proceeded more rapidly. Sections made on the fortieth and fiftieth days showed that the original callus had been transformed into dense compact bone similar to the old bone from which it could no longer be distinguished and with which it had intimately fused, whereas on the other side it still remained somewhat spongy and vascularized. Uffreduzzi concluded that periarterial sympathectomy seemed to stimulate and accelerate the normal rate of callus development and transformation.

Fontaine<sup>7</sup> performed several experimental studies on dogs. He symmetrically fractured the first metatarsal bones of two animals and performed a periarterial sympathectomy on the right side. He removed different segments of the fractured areas on the twentieth day and found that the fractures of both dogs were united and callus was well developed on the sympathectomized side. However, on the control side, the callus was much less pronounced, and abnormal mobility was still marked. In a third dog, a bilateral transverse fracture of the tibia was produced, and the fragments were held with bronze wire. Sympathectomy was performed on one side. Twenty-three days later, after the piece of wire had been removed, the side subjected to sympathectomy showed advanced union with good callus formation. No union existed on the control side.

Excision of the sympathetic ganglion is undoubtedly a more effective operation and is probably followed by better results than periarterial neurectomy. However, ganglionectomy is more difficult and hazardous, and it is extremely doubtful whether its application in fractures would be justifiable if simpler measures might prove almost as efficacious.

It was our purpose not only to determine the effect of periarterial sympathectomy on the healing of fractures of the leg, but also to ascertain whether evidence of vasodilatation could be demonstrated by injections of the arterial tree with a radiopaque substance. Histologic examinations were not made because this phase has been completely studied and confirmed by other observers and because roentgenologic findings alone are sufficiently satisfactory for the demonstration of the healing of bone and changes in vascularity.

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7. Fontaine, R.: *Rev. de chir.* 64:95, 1926.

Accordingly, a series of experiments was conducted on twenty dogs, but, owing to accidents of various kinds, only ten animals survived long enough to make the experiment complete.

#### TECHNIC

The main procedure consisted of simultaneously fracturing with a chisel both tibiae transversely at similar locations and then performing a unilateral femoral periarterial sympathectomy for 5 cm. of the vessel in Scarpa's triangle, the other extremity remaining as a control. Either 3 or 5 cc. of radiopaque iodized rape-seed oil<sup>s</sup> was injected into each femoral artery under direct vision. The entire vascular tree could easily and reliably be visualized by this procedure.

Roentgen studies of the fractures and freshly injected arterial system were made at regular intervals. Studies were made of the radiopaque vessels before

TABLE 1.—*Studies on Changes in Vascularity\**

No. of Dog	Before Sympathectomy (for Control)		Time Interval After Sympathectomy and Fracture	Left Sympathectomy: Both Legs Fractured		Right Leg		Left Leg		Comment. See Protocols
	Right Leg	Left Leg		Right Leg (Control)	Left Leg	Before Fracture	After Fracture	Before Sympathectomy	After Sympathectomy	
10598	0	0	2 wks.	+	++	0	+	0	++	Figures 6 and 7
10609	0	0	10 days	0	++	0	0	0	++	
10622	0	0	2 wks.	0	++	0	0	+	++	Figures 4 and 5
10625	0	0	3 wks.	+	+++	+	+	0	+++	
			6 wks.	—	++++	+	—	0	++++	
10678	0	0	2 wks.	+	++	0	+	0	++	
			35 days	+	+++	0	+	0	+++	
			2 mos.	+	++++	0	+	0	++++	
10655	0	0	2 wks.	+	+	+	++	+	++	Figures 1, 2 and 3
			2 mos.	n.c.	+++	n.c.	++	+	+++	
			2½ mos.	+	++++	+	—	+	++++	
10764	0	0	2 wks.	+	+++	+	+	0	+++	
10789	0	0	2 wks.	0	+++	0	0	0	++	

\* 0 indicates no change; +, an increase; —, diminished, and n.c., not comparable.

sympathectomy and before fracture. Similar studies were repeated after fracture and sympathectomy, and again at from seven to ten day intervals, and for varying periods up to ten weeks for vascular studies, and six months for the healing of bone.

The radiopaque substance used for injection was a heavy liquid consisting of 4 parts iodized rape-seed oil, with a specific gravity of 1.289, and 1 part of ethyl olive oil, making a specific gravity of 1.061.

It took considerable time and effort to so standardize the method of injection that satisfactory roentgenograms of the injected arterial tree could be regularly obtained. Attempts were made always to inject a uniform amount of iodized rape-seed oil at the same rate of speed in each experiment. When half of the oil had been injected, roentgen exposures were made while the remainder of the substance was being

injected. One great technical difficulty was caused by the fact that a needle of considerable bore had to be employed because of the viscosity of the iodized rape-seed oil. When injections had to be repeated on the same sympathectomized artery, the large needle would occasionally damage the wall of the neurectomized vessel, resulting in fatal hemorrhage.

A study of tables 1 and 2 and the protocols will reveal that the experimental procedure varied in details, especially as far as the time of the arterial injections were concerned. This was done to make every effort carefully to control the experiment. While the protocols are given in detail, the results of these experiments can best be appreciated by a study of tables 1 and 2, respectively.

TABLE 2.—*Studies on Callus and Bony Union*

No. of Dog	Callus			Bony Union			Comment: See Protocols
	Time Interval	Right Leg (Control)	Left Leg (Sympathectomy)	Time Interval	Right Leg (Control)	Left Leg (Sympathectomy)	
10609	1 mo.	None	++	(Death)			
10622	3 wks.	+	++	1 mo.	None	Union	Figures 4 and 5
10625	1 wk.	+	+	1 wk.	None	Partly Complete	
	2 wks.	++	+	2 wks.	None	Complete	
	6 wks.	+++	+	6 wks.	Fibrous	Complete	
10678	20 days	++	++	20 days	None	None	Figures 1, 2 and 3
	35 days	++	+++	35 days	None	Partial Complete	
	50 days	++	+++	50 days	None	Complete	
10685	20 days	+++	+	20 days	None	Union	
	40 days	+++	++	40 days	None	Union	
10765	2 wks.	+++	+	2 wks.	Fibrous	Complete	
10789	3 wks.	+	+++	(Death)			
10892	1 mo.	+	+++	1 mo.	None	Partial Complete	Figures 8 and 9
	2 mos.	++	+++	2 mos.	None	Complete	
10893	3 wks.	None	+	3 wks.	None	None	
	5 wks.	++	++	5 wks.	Partial	Partial Complete	
	6 mos.	++	++	6 mos.	Partial	Complete	

PROTOCOL 1 (dog 10598).—*Experimentation*.—Oct. 24, 1930: The right femoral artery was exposed in Scarpa's triangle and 5 cc. of iodized rape-seed oil was injected into it; roentgenograms of the lower extremity were then taken.

The left femoral artery was similarly exposed; 5 cc. of iodized rape-seed oil was injected, and roentgenograms of the extremity were taken.

October 28: The left femoral artery was again exposed in Scarpa's triangle and sympathectomized for 5 cm. of its extent; 5 cc. of iodized rape-seed oil was then injected. Roentgenograms were then taken.

The right femoral artery was then similarly exposed; 5 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

November 14: The right and left femoral arteries were again exposed, 5 cc. of iodized rape-seed oil being injected into each. Roentgenograms of each extremity were then taken.

November 28: The right femoral artery was exposed in Scarpa's triangle, and a sympathectomy was then done for a distance of 5 cm. Roentgenograms were then taken.

December 4: The animal died of secondary infection of a hematoma about the sites of the wounds. The tibial vessels of both sides were dissected out, and no gross difference was detected.

*Studies of Roentgenograms.*—Oct. 24, 1930: The injection of the left femoral artery was unsuccessful, but that of the right femoral artery was satisfactory.

October 28: The left vascular bed was greater than that of the right side and was increased over that of October 24.

The right vascular bed was increased over that of October 24.

November 14: The left vascular bed, the sympathectomized side, was definitely increased over that of the right side, and over that of October 28.

The right vascular bed remained unchanged from that of October 28.

November 28: After sympathectomy, the right vascular bed showed no change over the previous observation.

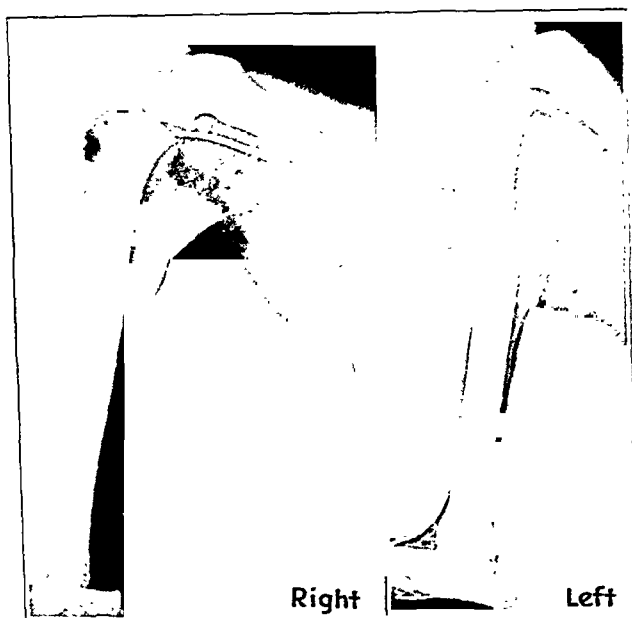


Fig. 1 (dog 10685).—Both legs were fractured. Sympathectomy was performed on the left side. Both femoral arteries were injected with iodized rape-seed oil. Many more small arteries are visible on the left than on the right.

*Comment.*—On referring to figures 6 and 7, it is seen that the richness of the vascular bed and the increase in the number and the caliber of the arteries are quite evident on the side of the sympathectomy (left leg).

*PROTOCOL 2 (dog 10699).—Experimentation.*—Oct. 31, 1930: The left femoral artery was exposed in Scarpa's triangle and 5 cc. of iodized rape-seed oil was injected; then roentgenograms of the lower extremity were taken. A periarterial sympathectomy was then done on the left femoral artery; 5 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. A lateral ligature was necessary to control the bleeding from the artery at the site of the needle puncture.

The right femoral artery was exposed in Scarpa's triangle, 5 cc. of iodized rape-seed oil was injected, and roentgenograms of the right lower extremity were taken.

Each tibia was then fractured by a chisel, through incised wounds at similar levels.

November 10: The left femoral artery was again exposed in Scarpa's triangle, and 5 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

The right femoral artery was again exposed, and 5 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

The left femoral artery was irretrievably damaged, causing an immediate fatal hemorrhage. After death, 3 cc. of iodized rape-seed oil was injected into each femoral artery, and roentgenograms were taken.



Fig. 2 (dog 10685).—Roentgenograms taken twenty days after those in figure 1. The union is almost perfect on the left side. The right leg (control) shows callus, but the line of fracture is not obliterated.

*Study of Roentgenograms.*—Oct. 31, 1930: The vascular bed on the left side before sympathectomy was slightly less than on the right side, but after the sympathectomy it was definitely greater. The left femoral artery, while not dilated, was larger in caliber than the right.

The fractures were found to be comparable.

November 10: There was a distinct increase in vascularity on the left side over the previous observation on October 31. The right side showed no change when compared with the observation of October 31.

On the left side there were no union and some displacement of the fragment. There was evidence of beginning callus formation along the ends of the fragments.

There were no displacement of fragments and no callus formation on the right side.

*Comment.*—The findings on the left side, when compared with those on the right side, seem to prove that the vascularity on the sympathectomized side was definitely increased.

The sympathectomized side alone showed callus formation. Bony union was not determined, as the animal died too soon.

PROTOCOL 3 (dog 10622).—*Experimentation.*—Nov. 18, 1930: The right tibia was fractured through a small incised wound at the junction of the upper and middle

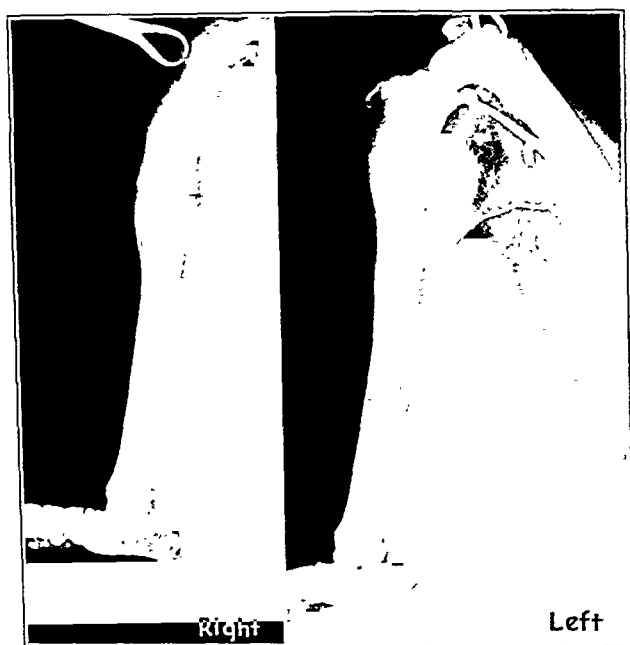


Fig. 3 (dog 10685).—Roentgenograms taken about two and one-half months after those in figure 2. There is complete healing on the left side. The right leg shows considerable callus. The fracture line is still unobliterated.

thirds. The right femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the right lower extremity were taken.

The left tibia was fractured at approximately the same site as the right. The left femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. A sympathectomy was then performed on the left femoral artery. The vessel immediately contracted.

November 28: Roentgenograms of both lower extremities were taken.

December 5: The wounds of both sides were healed.

The right femoral artery was again exposed in Scarpa's triangle, and was found to be embedded in organized fibrous tissue. Three cubic centimeters of iodized rape-seed oil was injected, and roentgenograms were taken.

The left femoral artery was then exposed and was found to be similarly embedded in organized adhesions. Three cubic centimeters of iodized rape-seed oil was injected, and roentgenograms were taken. A large hemorrhage resulted from the site of the injection, necessitating ligation of the artery and vein before it could be controlled.

December 12: Roentgenograms of both lower extremities were taken. The general condition of the animal was good, though the animal was unable to bear weight.

December 22: Roentgenograms of both lower extremities were taken.

April 20, 1931: The dog died.

*Study of Roentgenograms.*—Nov. 18, 1930: The left (sympathectomized) side showed a greater vascular bed than the right. The fractures were practically similar.

November 28: No injection was made.

The fracture remained similar. There was moderate callus on the left side, but none on the right side.

December 5: The left vascular bed showed an increase in general over the original observation of November 18.

The right side showed an increase in vascularity about the site of fracture, but not elsewhere. The left side, compared with the right, showed a marked increase in vascularity, especially about the fracture site.

The left side showed no increase in callus. The right showed beginning callus formation, which was definitely less than that on the left side.

December 12: There was marked callus on both sides, with a greater amount on the left side. The left side showed complete union, while the fragments of the right side were not united.

December 22: The left side showed a further increase in callus, with complete union. There was no change in the callus on the right side and no further union.

*Comment.*—This experiment again illustrates the decided increase in the vascularity of the left leg.

Within a three week interval, there was slight callus on the right side, but more callus on the left; furthermore, within a month's interval no bony union had taken place on the control side (right), and on the left side a firm bony union had already been established.

PROTOCOL 4 (dog 10625).—*Experimentation.*—Nov. 21, 1930: The right and left tibiae were fractured by a chisel through small incised wounds at similar levels. The right femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the lower extremity were taken. A sympathectomy was performed on the left femoral artery for 5 cm. of its extent, after the left femoral artery had been exposed, given an injection and x-ray similar to the right.

November 28 and December 5: Roentgenograms of both extremities were taken.

December 19: The left femoral artery was again exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. The right femoral artery was similarly exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

Jan. 6, 1931: Both femoral arteries were again exposed, 3 cc. of iodized rape-seed oil was injected into each vessel, and roentgenograms were taken.

March 10: Both femoral arteries were exposed and separately given injections of 3 cc. of iodized rape-seed oil, and roentgenograms were taken.

*Studies of Roentgenograms.*—Nov. 21, 1930: The right vascular bed was slightly greater than the left before sympathectomy. The fractures were not complete, but were similar and comparable.

November 21 and December 5: The fracture line on the left was almost obliterated.

On the right there was a small amount of callus.

December 12: The vascular bed after sympathectomy was greater on the left side than on November 21, and was more marked than on the right side.

On the right side, there was no change over the observation of November 21.

There was complete union on the left side. On the right side there was more callus, but partial union.

December 19: There was no change over the observation of December 12.

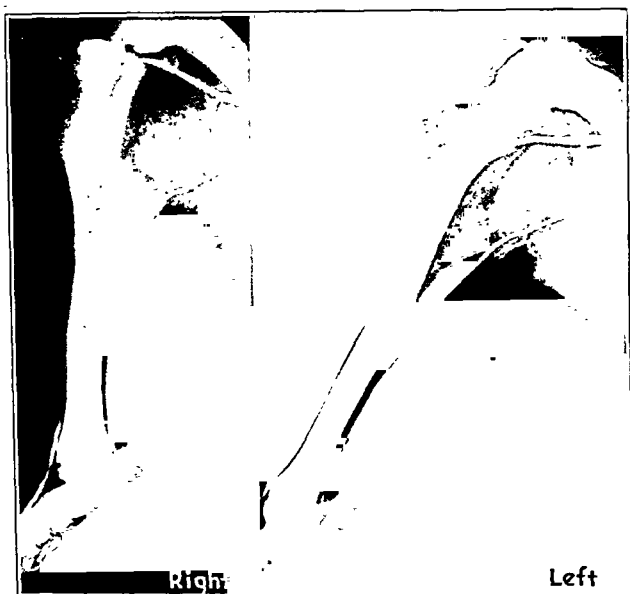


Fig. 4 (dog 10625).—Both tibiae were fractured. Sympathectomy was performed on the left. Note the richness in vascularity on the left side. The fracture line of the left tibia is not clearly shown here owing to underexposure.

Jan. 6, 1931: The left side showed a marked increase in vascularity which was greater than that on the right side. The right side showed a diminution in vascularity when compared with that of December 12. The left showed complete union. The right showed more callus but no union.

March 10: The injections were unsatisfactory and inconclusive. Both fractures were well healed, but resorption was more complete on the left.

*Comment.*—Three weeks after the left leg was sympathectomized, there was a decided increase in vascularity on that side. Note the complete bony union on the left in figures 4 and 5.

Findings during one-half and six week intervals showed more callus produced on the right. However, there was complete bony union on the sympathectomized side and only fibrous union on the control side.



Protocol 5 (dog 10678).—*Experimentation*.—Jan. 13, 1931: The right and left tibiae were fractured by a chisel through small incised wounds at similar levels. The right femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the extremity were taken.

The left femoral artery was similarly exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. Sympathectomy was then performed on the left femoral artery for 5 cm. of its extent.

January 27: Both femoral arteries were again exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil being injected into each. Roentgenograms were taken. There was a considerable amount of reaction about the sites of fracture, with a seropurulent discharge.

February 3: Roentgenograms of both lower extremities were taken.

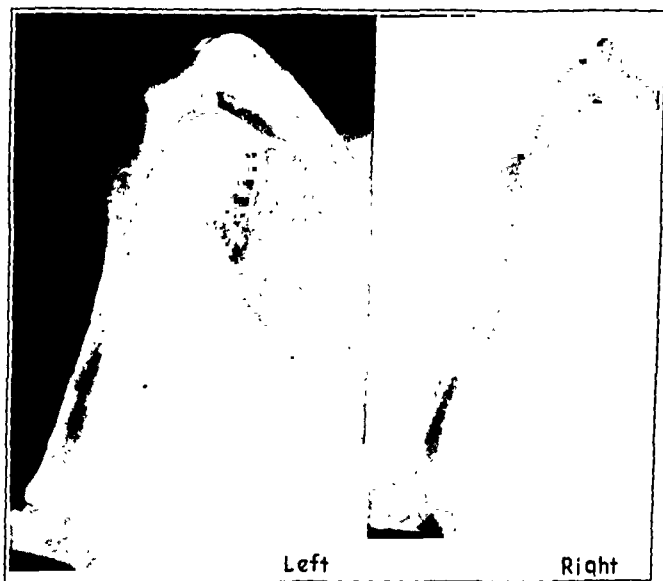


Fig. 5 (dog 10625).—Roentgenograms taken six weeks after those in figure 4. There is a marked increase in vascularity on the side of sympathectomy. Union is more complete on the left. (Unfortunately the injected main right arteries are not included in the print. The original films show them to be equally injected and comparable.)

February 17: Both femoral arteries were exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the lower extremities were taken.

March 3: Both femoral arteries were again exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. The dog was chloroformed on this date.

*Study of Roentgenograms*.—Jan. 13, 1931: The vascular beds of both sides were practically the same. The fractures were similar and comparable.

January 27: On the left (sympathectomized) side the vascular bed was decidedly increased over that on the right, and also over the original vascularity on the left side on January 13. The increase was especially about the fragments.

On the right side the vascular bed was increased over the observation of January 13, especially about the fragments.

February 3: Both sides showed an equal amount of callus; there was no evidence of union.

February 17: The vascular bed on the left showed a general increase over that of January 27, and was decidedly greater than that on the right side. Some of the vascularities showed an increase in caliber.

The vascular bed on the right showed an increase only about the site of fracture.

Both sides showed a definite increase in callus. The density and amount were greater on the left side, which also showed partial union.

March 3: The vascular beds remained unchanged over January 27, with the left side being greater than the right.

The left side showed an increase in callus and complete union. The right side showed a slight increase in callus and no union.

*Comment.*—Observations noted in three consecutive periods (table 1) seemed to show that there was a marked increase in the vascular beds on the sympathectomized side. It also was observed that the increase in vascularity was more pronounced in later experiments.

There was a considerable amount of callus about the fragment of the tibia in both legs, but it was more pronounced on the left, where the sympathectomy was performed. Observation was continued at twenty, thirty-five and fifty day intervals. At no time was there any evidence of union on the right side. Union commenced on the thirty-fifth day on the left side, and became complete in less than two months.

PROTOCOL 6 (dog 10685).—*Experimentation.*—Jan. 20, 1931: The right and the left tibiae were fractured by a chisel through small incised wounds at similar levels. The right femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. The left femoral artery was similarly exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken. A sympathectomy was then done on the left femoral artery for 5 cm. of its extent.

January 27: Roentgenograms of both lower extremities were taken.

February 3 and 10: Both femoral arteries were exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

February 24, March 31 and April 7: Both femoral arteries were exposed in Scarpa's triangle. Three cubic centimeters of iodized rape-seed oil was then injected into each, and roentgenograms of the extremities were taken.

*Studies of Roentgenograms.*—Jan. 20, 1931: There was no difference in the vascular beds of either side. The fractures were similar and comparable.

January 27: There was slight callus on the left side. On the right side there was no callus, and there was a slight separation of the fragments.

February 3: The vascular beds about the fragments were equally increased on both sides. There was no change on the left side with partial union. On the right side there was slight callus, without union.

February 10: There was complete union on the left, with an increase in callus. On the right there was no union. The callus was increased and was greater than that on the left.

February 24: On the left the injection was unsuccessful. On the right there was a definite increase in vascularity over February 3.

There was complete union with an increase in callus on the left. On the right there was no union. The callus was increased.

March 31: There was a definite increase in vascularity over the observation of the right and left sides on February 24.

On the right side, injection was unsuccessful, and the experiment was therefore not comparable.

The fracture line on the left side was obliterated. On the right, callus was increased, but there was no union.

April 7: The vascularity on the left side was greater about the fragments when compared with that side on March 31, and was greater than that on the right side.

The vascularity on the right side was diminished when compared with that on the right side on February 3.

Callus was slightly increased on the left, but was less than on the right. There was complete union, with obliteration of the fracture line.

The right side was unchanged. There was no union.

*Comment.*—At consecutive observations of two weeks, two months and two and a half months, the roentgen findings definitely showed an increase in vascularity

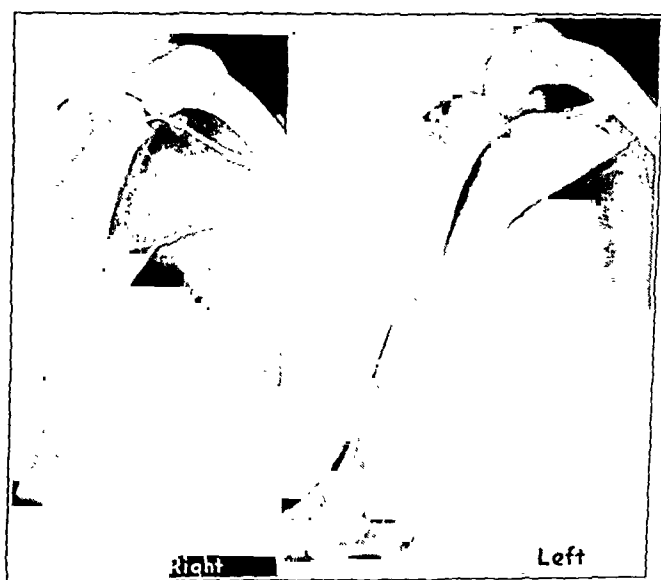


Fig. 6 (dog 10598).—Sympathectomy was performed on the left side. Note the relative richness in vascularity on the left side.

and dilatation of the capillary bed on the sympathectomized side. It is interesting to note that the vascular bed on the control side diminished considerably by the time of the last observation (figs. 1, 2 and 3). In addition, there was complete bony union on the side that had been sympathectomized, and there was no union on the control side.

PROTOCOL 7 (dog 10764).—*Experimentation.*—March 3, 1931: The right and left tibiae were fractured by a chisel through small incised wounds at similar levels.

The right femoral artery was exposed in Scarpa's triangle, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the lower extremity were taken.

The left femoral artery was similarly exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

A sympathectomy was then done on the left femoral artery for a distance of 5 cm.

March 10: Roentgenograms of both lower extremities were taken.

March 17: The left femoral artery was again exposed in Scarpa's triangle. While injecting the iodized rape-seed oil, the vessel ruptured, necessitating ligation to control the hemorrhage. Three cubic centimeters of iodized rape-seed oil was injected after this, and roentgenograms were taken.

The right femoral artery was exposed and ligated, and then 3 cc. of iodized rape-seed oil was injected. Roentgenograms were taken. The animal was then chloroformed. Specimens of the fracture sites were removed. The right side showed fibrous union, and the left side showed solid union. The femoral and tibial arteries were examined. The vessels of the left side were more dilated than those of the right side.

*Studies of Roentgenograms.*—March 3, 1931: The left vascular bed (sympathectomized side) was greater than the right. Both fractures were incomplete but comparable.

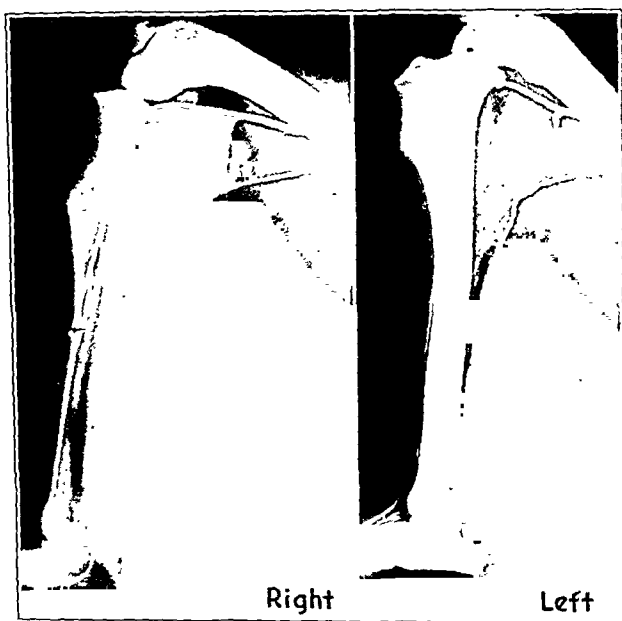


Fig. 7 (dog 10598).—Roentgenograms taken two weeks after those in figure 6. There is a further increase in vascularity on the left side.

March 10: There was no evidence of callus, and there was no change in the fractures.

March 17: The vascular bed on the left was definitely increased over the original observation.

The injection was unsuccessful on the right side.

There was evidence of callus on the right but none on the left.

*Comment.*—Two weeks after the control pictures were taken, the sympathectomized side presented a marked increase in vascularity. On the right side, however, there was very little increase in the vascular bed. These findings again emphasize that there appears to be a definite relation between vascularity and sympathectomy.

No deductions can be drawn on the question of callus and bony union, because the animal had to be chloroformed after two weeks of observation.

PROTOCOL 8 (dog 10789).—*Experimentation.*—March 10, 1931: The right and left tibiae were fractured by a chisel through small incised wounds at similar levels. The left femoral artery was exposed in Scarpa's triangle, and a sympathectomy was done for a distance of 5 cm.

March 24: The left femoral artery was again exposed in Scarpa's triangle, and 3 cc. of iodized rape-seed oil was then injected. Roentgenograms of the lower extremity were then taken.

The right femoral artery was similarly exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms were taken.

April 7: Each femoral artery was exposed, 3 cc. of iodized rape-seed oil was injected, and roentgenograms of the lower extremities were taken.

June 24: The animal died while being used for other experimental work.

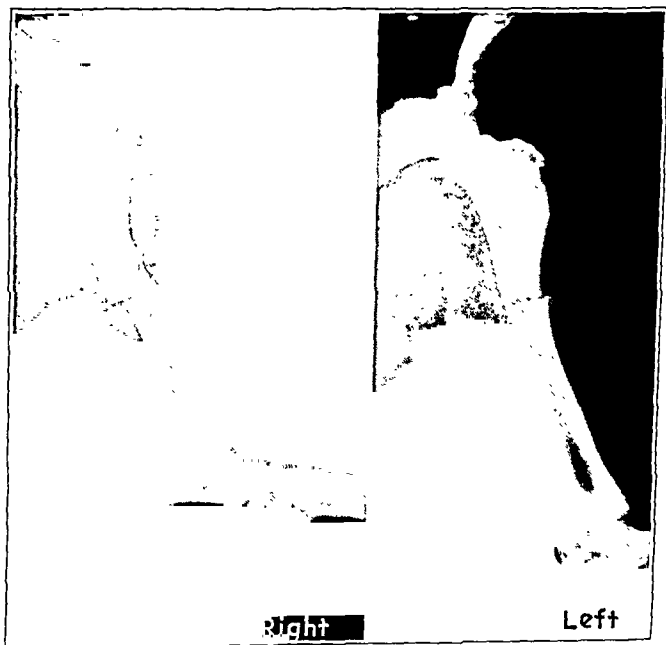


Fig. 8 (dog 10892).—Both legs were fractured. The left side was sympathectomized. Compare with figure 9.

*Studies of Roentgenograms.*—March 10, 1931: Both fractures were similar and comparable.

March 24: The vascular bed was greater on the left (sympathectomized) side than on the right.

No callus was present on either side.

April 7: The vascularity on the left was increased in amount, especially about the fragments, and was greater than that on the right.

The vascularity on the right was increased over that of March 24.

There was no increase in callus and bony union on the left side over March 3, but the callus was greater in amount than that on the right side. There was no union.

On the right, there was an increase in callus over the observation of March 24, but there was no union.

*Comment.*—After repeated studies, the nonsympathectomized side (the right leg) failed to show any change in the vascular picture, while the left side seemed to appear rich in the vascular bed.

There was considerable callus on the sympathectomized side (left). The study of the bony union could not be accomplished, owing to the death of the animal.

Protocol 9 (dog 10892).—*Experimentation.*—April 14, 1931: The left femoral artery was exposed in Scarpa's triangle, and a periarterial sympathectomy was done for a distance of 5 cm.

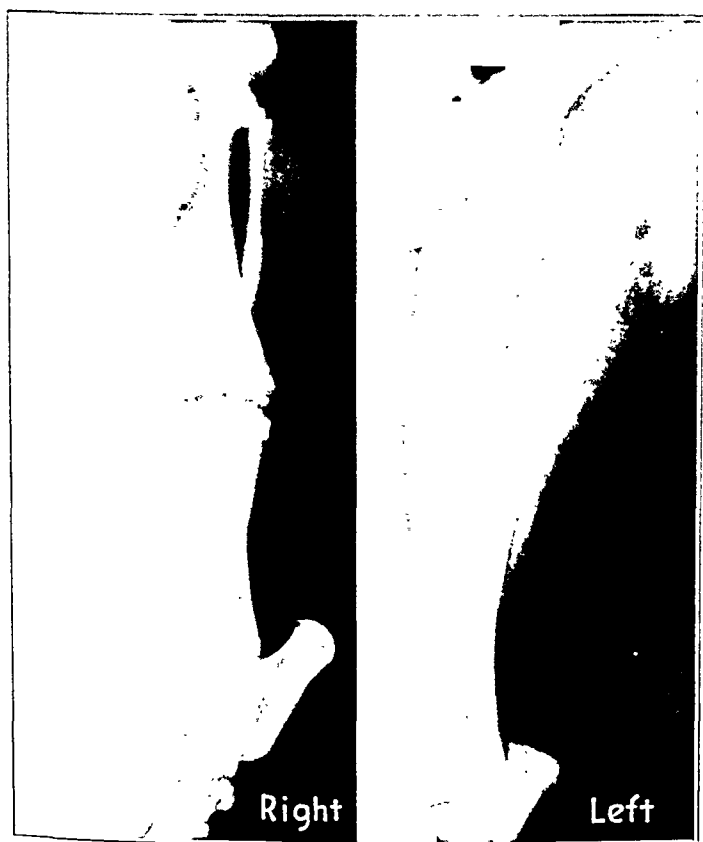


Fig. 9 (dog 10892).—Roentgenograms taken two months after those in figure 8. Both sides show marked callus, particularly on the left side. There is no bony union on the control (right) side. The left side shows union.

Both tibiae were fractured by a chisel through small incised wounds at similar levels. Roentgenograms of both lower extremities were then taken.

No injections of iodized rape-seed oil were made in this experiment. April 21 and 28, May 8, 15 and 22 and June 2 and 12: Roentgenograms of both lower extremities were taken.

August 14: The animal died after being used for other experimental work.

*Study of Roentgenograms.*—April 14, 1931: The fractures of both tibiae were complete and comparable.

April 21: The left (sympathectomized) side showed slight callus about the fracture; there was none on the right.

April 28: There was marked callus with partial union on the left. On the right, there was slight callus, but no union.

May 8: On the left, there was marked callus with partial union. On the right, there was little callus, but no union.

May 22: The roentgenogram of the left leg was unsatisfactory as the animal moved. On the right, there was a large amount of callus, but no union.

June 2: There was no change over the previous observation.

June 12: There was marked callus on the left, greater than on the right, with almost complete obliteration of the fracture line. On the right, there was marked callus, but no union.

*Comments.*—Observations were carried on at intervals of one and two months, during which time there was more callus on the left side than on the right. No union had taken place on the right side, but complete union had resulted on the left side (figs. 8 and 9).

PROTOCOL 10 (dog 10893).—*Experimentation.*—April 14, 1931: The left femoral artery was exposed in Scarpa's triangle, and a sympathectomy was done for a distance of 5 cm. Both tibiae were then fractured by a chisel at similar levels, through small incised wounds. Roentgenograms were then taken. No injections of iodized rape-seed oil were made in this experiment.

April 21 and 28, May 8, 15 and 22, June 2 and 12 and October 7 and 22: Roentgenograms of both lower extremities were taken.

*Studies of Roentgenograms.*—April 14, 1931: The fractures were complete and comparable.

April 21: There was no evidence of healing.

April 28: The fragments of both fractures showed overriding and separation, being more marked on the left side than on the right.

May 8: The left side showed slight callus and more overriding.

May 15: There was no change over the previous observation.

May 22: Both sides showed a large and equal amount of callus. There was partial union on both sides.

June 2: There was no change over the previous observation.

June 12: There was a slight increase in callus on both sides.

October 7: On the left, the fracture was completely healed, and the fracture line was obliterated. On the right, there was a slight deformity. The fracture line was still visible, and there was apparent union.

October 22: There was perfect healing with complete obliteration of the fracture line on the left side.

On the right side, there was complete healing, but the fracture line was still clearly visible.

*Comment.*—This dog was studied at intervals of three weeks, five weeks and six months. Both sides showed almost equal amounts of callus. There was no bony union at the end of the three week interval, but at the end of six months there was partial union on the control side and firm union on the left side, on which the sympathectomy had been performed.

#### SUMMARY

Radiopaque visualization of the arterial tree of the lower extremity on which a femoral arterial sympathectomy was performed at Scarpa's

triangle revealed an increasing vascularity in all experiments. This persisted throughout the longest period of observation, that is, ten weeks.

Callus was first detected on the sympathectomized extremities in five dogs, three times on the control extremities, and in one instance, it was doubtful. Firm bony union, however, was evidenced sooner on the sympathectomized side in all animals surviving a sufficient period of observation. Complete bony union, as determined by obliteration of the fracture line, occurred only on the sympathectomized extremity and was never noted on the control side during the period of observation.

#### COMMENT

The experimental work of others and this study seem to prove that periarterial sympathectomy has a physiologic basis for clinical application in the problem of the repair of fractures. In a series of clinical cases previously reported,<sup>9</sup> femoral periarterial sympathectomy in Scarpa's triangle was performed on seven patients with recent fractures of both bones of the leg. There was a diminution in time of eleven days in obtaining clinical union, and of nineteen days in hospitalization. No case showed a tendency toward delayed union when compared with a control series. In a group of ten cases of delayed union in fractures of the lower extremity which were ununited after an average of seventy days, clinical union resulted twenty-one days after sympathectomy in eight cases.

#### CONCLUSIONS

1. These experiments of femoral arterial injection seem to show quite definitely that an increased vascularity results from periarterial sympathectomy and that this procedure accelerates bony union.
2. The experimental and clinical evidence seems to justify a further trial of this operation in recent fractures, in those regions in which delay in union is characteristic and in those fractures in which union appears to be delayed.

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9. Colp, R., and Mage, S.: Experiences with Periarterial Sympathectomy in Fractures of the Lower Extremity, *J. A. M. A.* **97**:1069 (Oct. 10) 1931.



# TREATMENT OF PULSATING EXOPHTHALMOS

WITH REPORT OF TWO CASES

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Pulsating exophthalmos, or retrobulbar arteriovenous aneurysm, a lesion first reported by Benjamin Travers in 1809, is a relatively rare condition meriting report whenever seen. An average of about five cases is reported each year. Harkness<sup>1</sup> collected six hundred and twenty-one cases from the literature in his paper published in May, 1930. An exhaustive review of the literature is not attempted here, that angle of the problem having been dealt with ably by de Schweinitz and Holloway,<sup>2</sup> later by Locke<sup>3</sup> and still later by Harkness.

Diagnosis of the lesion usually may be made from the patient's history and appearance alone. The history is fairly typical: After trauma resulting in a period of unconsciousness, the patient has failure of vision or blindness in one eye, unilateral exophthalmos and a rushing, roaring sound in the head synchronous with the pulse. Palpation of the eye commonly discloses a thrill, and auscultation, a bruit synchronous with the pulse.

Autopsy in these cases usually reveals an opening in the internal carotid artery in its course through the cavernous sinus. The lesion tends to be progressive rather than tending to a spontaneous cure, although some cases apparently have cleared spontaneously (Noland and Taylor<sup>4</sup>).

The time-honored treatment of pulsating exophthalmos has been ligation of the artery involved, either abruptly or gradually. Sudden ligation of the internal carotid artery is attended with a high percentage of hemiplegia and other evidences of unilateral cerebral damage. This has led to ingenious devices for closing the artery gradually. An

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From the Cleveland Clinic.

1. Harkness, G. F.: *Intracranial Arterio-Venous Aneurysm, Pulsating Exophthalmos*, *Internat. J. Med. & Surg.* **43**:243, 1930.

2. de Schweinitz, G. E., and Holloway, T. B.: *Pulsating Exophthalmos: Etiology, Symptomatology, Pathogenesis and Treatment*, in *Diseases of the Eye: A Handbook of Ophthalmic Practice*, ed. 10, Philadelphia, W. B. Saunders Company, 1924.

3. Locke, C. E., Jr.: *Intracranial Arterio-Venous Aneurysm or Pulsating Exophthalmos*, *Ann. Surg.* **80**:1 and 272, 1924.

4. Noland, L., and Taylor, A. S.: *Pulsating Exophthalmos: Result of Injury*, *Tr. South. S. A.* **43**:171, 1931.

excellent account of these methods is given by Hanford and Wheeler.<sup>5</sup> Other operators have ligated the common carotid artery, retrograde flow from the external to the internal carotid usually being sufficient to prevent cerebral complications. The résumé by Hanford and Wheeler reports 67 per cent of patients cured and 83 per cent cured or improved by primary ligation of the internal carotid artery. After ligation of the common carotid, 46 per cent of patients were cured, and 64 per cent were cured or improved. Locke's statistics were about the same in 1924.

In considering a rational treatment for intracranial arteriovenous aneurysm, one should take into account the principles of treatment of arteriovenous aneurysm elsewhere, as in a leg or an arm.

#### PRINCIPLES OF TREATMENT

*Principle I.*—The Hunterian principle of ligation of the involved artery proximal to the fistula (fig. 1 *b*) has long been recognized as inadequate, since collateral circulation promptly bridges over the ligature. Applied to pulsating exophthalmos, this involves ligating the ipsilateral internal or common carotid artery. Ligating the common carotid artery allows a greater degree of anastomosis to continue the lesion, although the immediate morbidity from cerebral accident is lessened.

*Principle II.*—Ligation of the artery both proximal and distal to the aneurysm (fig. 1 *b* and *c*) may be beneficial when there are very few collateral channels. In these intracranial lesions, the ligatures would be applied to the internal carotid artery in the neck and within the cranium between the circle of Willis and the cavernous sinus (fig. 2 *a* and *c*). The intracavernous portion of the internal carotid artery gives off the ophthalmic artery and a few minute twigs, one anastomosing with the middle meningeal artery and the remainder supplying the pituitary gland. It is by way of these anastomoses that this principle of treatment may be defeated in this lesion.

*Principle III.*—Ligation of all the arteries and veins involved in the lesion (fig. 1 *b*, *c*, *d*, *e*, *f* and *g*) has proved, in general, to be the principle of greatest efficacy in treating arteriovenous aneurysm. In the case of pulsating exophthalmos, this would involve ligating the internal carotid artery above and below the cavernous sinus, ligating the ophthalmic artery and isolating by ligature the ipsilateral cavernous sinus. Ligation of the internal jugular vein with the internal carotid artery has been advocated by many writers. This is incomplete as the two cavernous sinuses, unfortunately, communicate through the anterior and posterior intercavernous sinuses, ligation of which would be extremely difficult, if not technically impossible, at present. It seems, then, that the principle most efficacious in controlling other arteriovenous fistulas would fail to be applicable in this instance.

5. Hanford, J. M., and Wheeler, J. M.: Pulsating Exophthalmos, Ann. Surg. 92:8, 1930.

*Principle IV.*—Direct closure of the fistula (fig. 1 *a*), while theoretically the method of choice, is rarely feasible in arteriovenous fistulas. In retrobulbar arteriovenous aneurysms actual ligation obviously is impossible within the cavernous sinus. A method of occlusion has been devised by Brooks<sup>6</sup> of Nashville, and has been used by other operators with apparent success, although at present its status is not definitely fixed.

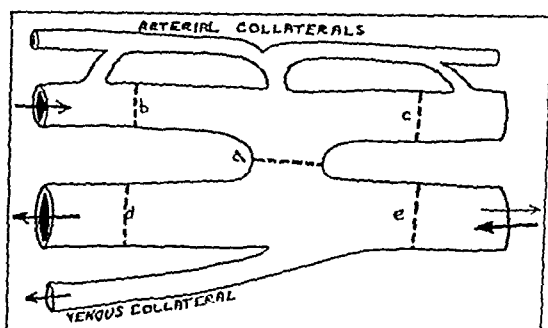


Fig. 1.—Diagrammatic representation of ligations used to control arteriovenous aneurysm.

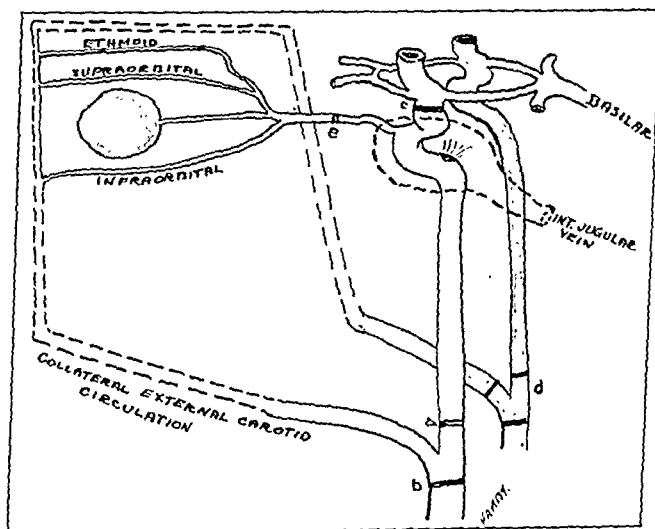


Fig. 2.—Diagram of circulation involved in retro-orbital pulsating exophthalmos and collaterals.

Brooks opened the internal carotid artery in the neck, between clamps, and packed long thin strips of muscle into the artery. The incision in the artery was then closed, and the clamps removed; the blood stream forced the muscle into the fistula, effectually plugging it. The eye in the case described was later lost from thrombosis. In adopting

6. Brooks, C. M., in discussion of Noland and Taylor.<sup>4</sup>

Brooks' technic, we used a smaller muscle embolus, hoping to have the function of the artery, but ligation was necessary later.

This seems a rather radical procedure—sending a muscle embolus toward the brain with all the force of the heart behind it. The embolus is propelled by a force equal to the systolic blood pressure (fig. 3). At the fistula, however, it is acted on by two other forces; at the point of division it may go into the cerebral circulation, against a pressure equal to diastolic blood pressure or 80 mm. of mercury, or it may go into the fistula, where the pressure is very much lower. The embolus takes the course of least resistance and enters the fistula. If it is not large enough to engage the margins of the fistula, it is held by the lacework of fibers in the sinus and can go no further. The combined effect of the embolus and resulting thrombosis closes the opening.

Mechanical devices which accomplish compression of the arteries in the neck by various ingenious pressure bands and springs have maintained many patients in a fair state of health, as in one case reported by Harkness. Another expedient is ligation of the common carotid artery, allowing retrograde blood flow to prevent sudden anemia of the brain, and later ligation of all the branches of the external carotid artery

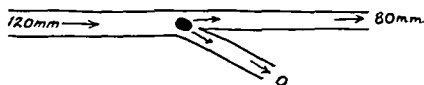


Fig. 3.—Mechanics of blood flow at point of arteriovenous fistula.

except the internal maxillary and temporal, thus further diminishing the blood flow by reducing the number of anastomoses. This was advocated by Dorrance.<sup>7</sup>

Of course, many patients are considered cured if they are able to continue with their daily routine in fair comfort even though the bruit is still faintly audible with the stethoscope, but the lesion cannot be considered absolutely cured until the fistulous opening is closed. The lesion tends to be progressive and will recur unless the fistula is closed, or the involved vessel is isolated from the general circulation.

All spontaneous cures of these fistulas have been by thrombosis, vision of the ipsilateral eye being lost. The majority of patients having this lesion are blind from the outset, and blindness practically always results from later thrombosis of the cavernous sinus. Any method of treatment that requires thrombosis will result in a high incidence of blindness. If retrograde flow can be induced through the branches of the ophthalmic artery and vein from their external carotid anastomoses, it might be possible to ligate these vessels proximal to their branches (fig. 2 c) and establish an entirely new ophthalmic circulation. This probably would save the eye.

7. Dorrance, G. M.: The Operative Treatment of Pulsating Exophthalmos, *Am. J. Ophth.* 13:675, 1930.

Before operating on these patients by any method, a period of preliminary carotid compression must be instituted for the purpose of encouraging collateral circulation through the circle of Willis and to accustom the ipsilateral cerebral hemisphere to changes in arterial blood pressure. By this procedure the incidence of hemiplegia has been greatly reduced. At first the patient may not be able to stand more than one or two minutes of compression before feeling dizzy or faint. Compression is promptly stopped, but is repeated in increasing lengths of time, every three hours, until the patient can bear from thirty to forty-five minutes of occlusion without signs of cerebral damage. The pulsations of the carotid are felt; then the artery is pressed backward and inward against the transverse processes of the lower cervical vertebrae. The bruit should be listened for to determine whether or not occlusion is complete. While various mechanical devices have been designed for this purpose, digital compression is probably the most reliable.

Two cases are presented demonstrating the application of several combinations of the previously outlined principles of treatment.

#### REPORT OF CASES

CASE 1.<sup>8</sup>—A woman, aged 32, entered the clinic on April 17, 1931, complaining of blindness in the right eye, protrusion of the eye and a constant swishing roar in the head synchronous with the pulse. On Feb. 6, 1931, she had received a severe blow on the right supra-orbital area in an automobile accident, the lacerations caused by this requiring suture. She immediately became unconscious and remained so for six days. On regaining consciousness, she was blind in the right eye, and a roaring noise was heard, which had been present constantly since. Hearing was diminished on the right side, and the patient was dizzy.

Examination revealed a right pulsating exophthalmos with a systolic bruit and blindness. There was a palsy of the sixth nerve on the right side, and the pupils were irregular, the right being larger than the left. The left pupil reacted to light and in accommodation normally; the right consensually only. The palpebral fissures measured 11 mm. on the right and 8 mm. on the left. There was a severe degree of conjunctival edema in the right eye with engorgement of the retinal vessels and atrophy of the optic disk. The only other finding of significance was a positive Romberg sign.

Lumbar puncture revealed an initial pressure of 110 mm. of water, a normal response to Queckenstedt's test and clear, colorless fluid. The spinal fluid showed a faint trace of globulin, with a colloidal gold curve of 5555521000; the Wassermann and Kahn reactions were 4 plus; the total protein was 30 mg. per hundred cubic centimeters of fluid. The Wassermann reaction of the blood was 4 plus in three antigens, and the Kahn reaction, 2 plus.

A roentgenogram of the right orbit showed erosion of the superior inner margin of the orbit. Other laboratory tests gave normal findings.

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8. This case was reported originally in the *Cleveland Clinic Quarterly (A Case of Traumatic Retrobulbar Arteriovenous Aneurysm, January, 1932, vol. 1, no. 1)*.

The patient was started on antisyphilitic treatment. It was found that digital compression of the right common carotid artery against the carotid tubercle made the patient dizzy and weak after two or three minutes, but it stopped the roar in her head and stopped the pulsation of the exophthalmos. To accustom her to diminished blood supply through the cerebral arterial system, digital compression was applied to the artery several times daily until, twenty-five days after she entered the hospital, she could tolerate compression for twenty-five minutes with ease.

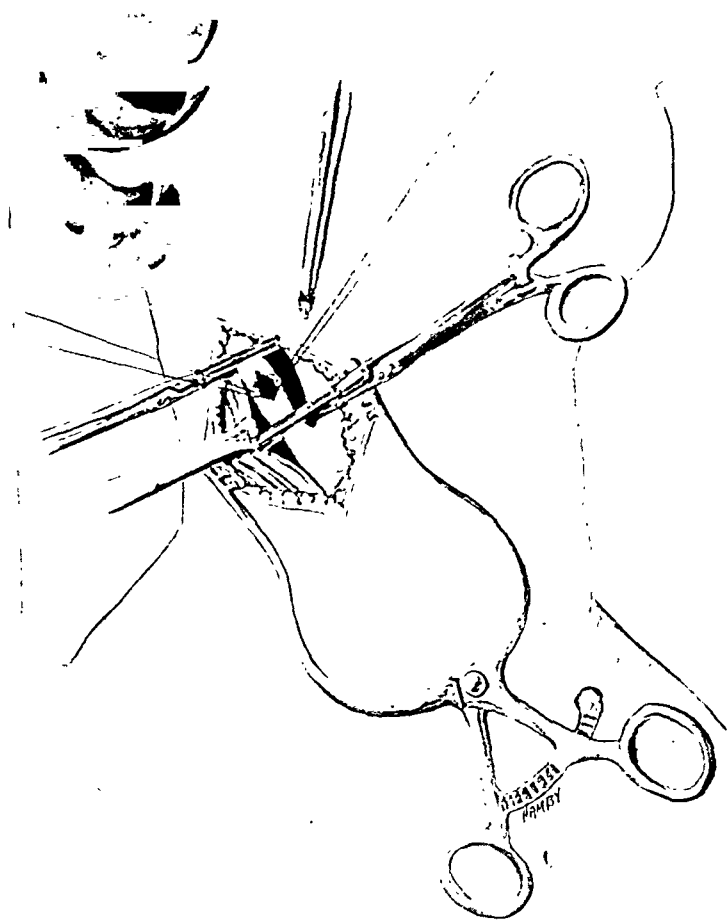


Fig. 4.—An insertion of muscle plug into internal carotid artery.

It was decided to attempt a direct occlusion of the fistula by the method of Dr. Brooks.

On May 15, the patient was operated on (fig. 4). Under local anesthesia, a 3 inch (7.6 cm.) incision was made just in front of the anterior border of the sternocleidomastoid muscle on a level with the thyroid cartilage. The common carotid artery with its bifurcation was exposed. Compression of the external carotid did not affect the bruit, while compression of the internal carotid stopped it completely. The internal carotid was then dissected free for a distance of 4 cm. and was clamped with two rubber-shod artery clamps. A vertical incision about 1 cm. long was made into the lumen of the artery between the clamps. A purse-

string suture of silk was placed around the incision, after which a piece of muscle was removed from the platysma, cut to the size of a pea and clamped with a small silver hemostatic clip. This was tucked into the opening in the artery. The purse-string suture was tied and was oversewed with two additional running silk sutures. The clamps were removed and the artery replaced in its bed. The patient noticed no recurrence of bruit following the removal of the clamps, which had been left on for about twenty minutes with no untoward effects. A tape treated with petrolatum was put around the internal carotid artery to allow for traction hemostasis in the event that the arterial sutures failed to hold. This was removed twenty-four hours later. The wound was closed with buried silk and with clips to the skin. The patient's condition and morale were excellent throughout.

Roentgenograms showed the silver clip which had been attached to the muscle embolus to be in the right side of the skull just to the outer side of the dorsum sellae and on a level with its floor (fig. 5).

The patient was kept in bed, and quiet was strictly enforced. She complained of headache and had some emesis for two days, probably the result of the changes in cerebral blood flow.

On the third day, a thrombus was palpable in the upper lid, and chemosis of the conjunctiva was becoming prominent. On the sixth postoperative day, a bruit became audible with the stethoscope, but it was much less than it had been a week previously. The patient had not heard the bruit since the operation.

On July 8 (fifty-three days after operation), the patient was readmitted to the hospital. Her progress had been excellent, but the bruit had become audible to the patient a short time before.

On examination, the right eye looked much better, not so large or injected. The palpebral fissure on the right was 9 mm., wider by 1 mm. than on the left. There was almost complete atrophy of the right disk. The bruit was audible, but there was no palpable thrill.

In this case, the muscle plug and subsequent thrombosis had almost obliterated the fistula. Knowing the progressive nature of these lesions, it was decided further to diminish the blood supply with the hope of obtaining a complete cure.

On July 9, under gas and local anesthesia, the right common and internal carotid arteries were ligated. The patient progressed very satisfactorily. She had some headache at times, but the bruit was inaudible at all times. She was discharged on July 17. She has continued antisyphilitic treatment intermittently, since she is living away from medical attention and is not able to get to a physician often.

We last saw her on April 7, 1932. At that time there was no audible bruit. There was absolute atrophy of the right disk, and the difference in the width of the palpebral fissures was 1.5 mm. Her condition was excellent, and she had no complaints.

The second case of pulsating exophthalmos proved interesting on account of the rapid development of anastomoses after ligation of the vessels.

CASE 2.—A rather obese woman, aged 48, was first seen at Charity Hospital on Sept. 27, 1931. She had fallen from a balcony thirteen weeks before, striking her head on a concrete sidewalk, and had been rendered unconscious. She had remained in that state, or semiconscious, for three days. Roentgenograms disclosed a linear fracture of the right frontal region. On regaining consciousness, she had been aware of a "rushing," throbbing sound on the left side of the head. The right eye, which had been greatly congested and discolored at first, rapidly improved.

There was no extra-ocular palsy at that time. As convalescence progressed, vision in the left eye began to fail, conjunctival edema and protrusion of the left eye developed, and she had severe headache.

Examination disclosed marked venous congestion of the left conjunctiva and lids and marked left conjunctival chemosis. There was a loud bruit over the left eye, synchronous with the pulse. This could be controlled entirely by compression of the left common carotid artery. There was complete paralysis of the left sixth

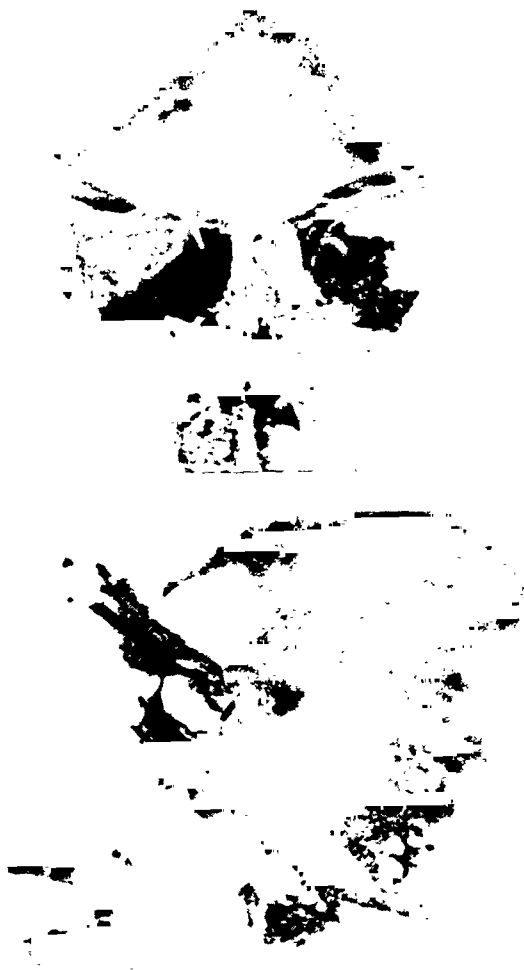


Fig. 5.—Roentgenograms of skull, showing clip in place. Upper picture, anterior view; lower picture, lateral view.

nerve and partial paralysis of the third and fourth nerves. There was some hypalgesia over the area of distribution of the first division of the left fifth nerve. The other cranial nerves functioned normally.

The diagnosis was pulsating exophthalmos, with the fistula between the internal carotid artery and the cavernous sinus, and paresis of the left second, third, fourth, fifth and sixth nerves.

To accustom the patient to diminished cerebral blood supply and to allow the other vessels to compensate, digital carotid compression was applied every three hours, starting with one minute, then increasing as rapidly as possible. She became



able to stand thirty minutes of compression without discomfort. It was then proposed to insert a muscle embolus into the artery as in the previous case.

Operation was performed on October 9 at Charity Hospital. The left internal carotid artery was exposed, elevated and compressed, and the bruit was controlled completely. The artery was dissected for a distance of 3 cm., and a rubber-shod artery clamp was placed at each end of this area. Owing to technical difficulties, however, the attempt to insert a muscle embolus was unsuccessful, so the vessel was ligated and cut. The common carotid was exposed and ligated below its bifurcation, and the incision was closed. A pressure bandage was applied to the eye for twenty-four hours. The bruit was still faintly audible with the stethoscope, but was not heard subjectively.

Eighteen days later, auscultation disclosed a faint bruit, although the patient was not conscious of its presence. There were still paralysis of the left sixth nerve



Fig. 6.—Intracranial ligation of left internal carotid artery. Frontal lobe retracted; ligature around internal carotid artery.

and paresis of the third nerve. Exophthalmos had cleared up, chemosis had disappeared, and there was no palpable thrill. A thrombus was palpable in an orbital vessel just above the outer canthus.

The patient was readmitted to the hospital on March 30, 1932, four and one-half months after the first operation. She had been well since her last visit, but the headache had been increasing in severity, and vision was failing at times in the left eye, although frequently it was better than in the right. The bruit was audible subjectively at intervals.

Examination disclosed that the patient had lost some weight, but she looked much better. There were moderate dilatation and congestion of the left scleral vessels, but no thrombosis; they could be emptied by pressure. The two eyes were of about the same size. There was a loud bruit in the left eye, in the left frontal and maxillary regions and, to a lesser extent, over the right globe. Pressure on the right carotid failed to stop the bruit.

Examination showed a normal right fundus, while the left showed marked tortuosity of the retinal vessels with a small amount of papilledema. The visual fields were full.

The bruit following the ligation of the left carotid artery came, of course, from retrograde blood flow through the circle of Willis and down into the injured vessel. This flow could be controlled at first by shutting off the right carotid flow. The vertebral and basilar arteries later enlarged, until they were transmitting enough blood to cause bruit without the carotid contribution. It was proposed, then, to ligate the artery intracranially between the cavernous sinus and the circle of Willis.

On March 31, an encephalogram was taken for the dual purpose of draining the cerebrospinal fluid and of determining the amount of cerebral damage resulting from trauma and the lesion. The plates disclosed only traumatic pia-arachnoid adhesions over the right cerebral hemisphere.

On March 31, a left frontal craniotomy was performed as for an approach to the sellar region. The left internal carotid artery was ligated with a double silk ligature just above the cavernous sinus, leaving the circle of Willis intact. Following the operation, no bruit was audible in either eye. The next morning, however, the bruit was audible faintly both subjectively and objectively over both eyes. Pressure on the right carotid artery controlled it completely. The recurrence of the bruit was a great disappointment, of course, but since these lesions are known to be progressive rather than tending to cure, it was felt that further intervention should be attempted.

Within the sinus, the internal carotid artery gives off one large vessel, the ophthalmic, and several minute twigs, one of which anastomoses with the middle meningeal, the others supplying the pituitary gland. Since the ophthalmic is the largest of these, it was reasonable to assume that its anastomoses were responsible for the retrograde flow. Several operators (Hanford and Wheeler) have ligated the ophthalmic artery and vein within the orbit as a part of their attack on these lesions. The ophthalmic anastomoses with the external carotids through a number of branches, the most important being the supra-orbitals and infra-orbitals and the ethmoid. The left external carotid was already occluded. All these other anastomoses were supplied by the opposite external carotid. A period of daily right carotid compression was then started, and finally the patient could tolerate, with ease, pressure for thirty minutes every three hours.

On April 11, fourteen days after the craniotomy, the right common artery and the internal and external carotid arteries were ligated at the area of bifurcation. This procedure stopped all bruit, objective and subjective, and the patient had no further complaints except an occasional slight headache. She was allowed out of bed six days after operation; she had no dizziness or other cerebral symptoms and was discharged on April 23, twelve days after ligation of the right carotid artery and twenty-three days after craniotomy.

#### COMMENT

Unfortunately, most of us see so few of these cases that each is a new experience when it confronts us. It is obvious, however, that the "routine" treatment by ligation of a carotid artery is inadequate completely to cure this lesion and that rational, effective treatment is yet to be determined. These cases demonstrate that such a progressive lesion often requires a progressive attack, and that it should be energetically dealt with until such a time as a successful outcome seems assured.

# SURGICAL ASPECTS OF RENAL AGENESIS

## WITH SPECIAL REFERENCE TO HYPOPLASTIC KIDNEY, RENAL APLASIA AND CONGENITAL ABSENCE OF ONE KIDNEY

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NEW YORK

Among the most enigmatic surgical anomalies of the upper urinary tract which interest the medical profession and particularly the surgical specialist are the three much confused borderline conditions of hypoplastic kidney, renal aplasia and congenital absence of one kidney. All of these have clinically the same common denominator, in that when the supposedly sound kidney is removed at operation for an associated pathologic process, the outcome is promptly and inevitably anuria and death. But fortunately, the time has come when these three very hazardous and unrecognized conditions of the past can be differentiated and accurately identified before postmortem examination.

A survey of the literature on this rather obscure subject reveals that the underlying cause of such a compromising situation is an embryonic malformation and lack of proper development of the urinary organs, which is also commonly associated with developmental defects of the genital organs. The problem is further confused by lack of proper classification, due to failure to recognize many of these cases and to the impossibility of obtaining sufficient clinical data. Many authors who have written on this subject have not had a clear conception of these three unusual conditions and have often confused them with a secondary or acquired type of atrophy of the kidney, when in reality one is dealing with an arrest of development of the organ. A solitary kidney or atrophy of one kidney has been rather commonly found at postmortem examination. Various authors, in reporting a long series of autopsies totaling 92,690, give the relative frequency of hypoplastic kidney as 1 in 600, that of renal aplasia as 1 in 400 and that of solitary kidney as 1 in 1,600. The clinical ratio has never been accurately established, because, prior to the era of cystoscopy and pyelography, the preopera-

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From the Department of Urology, James Buchanan Brady Foundation of the New York Hospital.

tive or antemortem diagnosis was seldom made; consequently, the cases found at operation or on the dissecting table have been surprisingly numerous. It is necessary at this time to specify that in this study I shall not discuss the condition recorded by many authors as congenital or acquired atrophy of the kidney, when the atrophy is due to disease, trauma or an associated pathologic process in which the kidney undergoes complete destruction, losing its renal parenchyma and becoming functionless, as commonly occurs in tuberculosis, hydronephrosis, pyonephrosis or stone long impacted in the ureter. In this paper I shall deal exclusively with the variety of congenital malformation in which one kidney is absent, or there is a rudimentary or infantile type of kidney, or an arrest occurs in the development of the organ, which is consequently incapacitated to sustain life. It is obvious that while this condition is of clinical interest to the embryologist and pathologist, it is of even greater importance to the urologist and the surgeon. The only lesion with which I am concerned in this study is the unilateral type, since when the condition is bilateral it has no clinical interest, in that it is at the outset incompatible with life.

The best conception of this malformation of the upper urinary tract is that it represents an embryonic defect or lack of development during intra-uterine life, when the organ in its evolution did not develop to its full extent or the wolffian duct of the mesonephros failed to produce a renal bud after the duct had reached the cloaca, as in the case of unilateral renal agenesis. The variation in the evolution and mechanism of the migration, ascent and rotation that these organs undergo from their position in the bony pelvis behind the cloaca to the lumbar region in the adult explains the multiplicity of variations of congenital malformations that may be encountered. In studying the surgical aspect of congenital anomalies of the kidney, one cannot fail to be tremendously impressed with their frequency, particularly in a routine urologic practice, since they constitute about 40 per cent of all pathologic lesions of the kidney. Hence proper clinical recognition is of extreme value, not only for establishing a correct diagnosis but also to assure a sound prognosis.

In reporting eight cases to illustrate these three varieties of renal agenesis, which I have had the opportunity to study at the urological department (James Buchanan Brady Foundation) of the New York Hospital, I shall discuss first the most important points in the pre-operative diagnosis. Secondly, I shall emphasize the value of a complete and careful urologic and urographic examination in order to avoid the dangerous surprise that is involved in this renal hypoplastic, or aplastic, or agenetic condition. It is also my purpose to point out the surgical aspect of this problem and its proper treatment.

Since it is obvious that the borderline differentiation between these three clinicopathologic conditions of the kidneys has not been mentioned

in any textbooks, and since this is indeed not easily recognized, the problem it presents is often not adequately solved. It seems proper, therefore, to study the three conditions separately, while describing the illustrative cases of each modality. In an attempt to abbreviate this communication and to make it of more practical interest, I have summarized its main points in the following tabulation, basing my classifications on the most important clinicopathologic and cysto-uropelographic data as a means of differentiating these three unique conditions of the undeveloped kidney. The three descriptive classifications which I have worked out with a view to facilitating a correct diagnosis will serve to establish greater accuracy in their clinical and anatomopathologic description and their proper differentiation.

*Classification and Clinicopathologic Differentiation of Hypoplastic Kidney, Renal Aplasia and Congenital Absence of One Kidney*

Hypoplastic Kidney

1. Small or infantile in type; other kidney hypertrophic
2. Normal renal parenchyma
  - (a) With medullary and cortical substance
  - (b) With absence of pyramidal substance
3. Microscopic sections reveal normal or rudimentary glomeruli and tubules
4. Rudimentary or hydronephrotic pelvis
5. Calices bizarre in position and size, sometimes absent
6. Patent ureter
7. Normal urine secretion
8. Diminished or normal renal function
9. Good urea excretion and phenolsulphonphthalein elimination
10. Pyelography and roentgenography reveal hypoplastic kidney or diminutive organ

Renal Aplasia

1. No true kidney
2. No evidence of pelvis
3. Absence of true renal pedicle
4. Renal artery small or absent
5. Ureter incompletely developed and not patent
6. No excretion of urine
7. No renal function
8. Bladder with two normal ureteral orifices or one ectopic ureter
9. Histologic section of the supposed renal mass reveals glomeruli and tubules, showing arrest of development of renal organ
10. Cystoscopy, catheterization of ureters and descending or ascending pyelography for diagnosis of the condition

Congenital Absence of One Kidney (Congenital Solitary Single Kidney)

1. No evidence of hypoplastic or aplastic renal tissue
2. Complete absence of a mate with hypertrophy of the solitary kidney
3. Single kidney with double pelvis and double ureters, or
4. Kidney with single or double ureters in cross ectopia

5. Vesical trigone distorted or absent
6. Bladder with one ureter or two openings in one side
7. Suprarenal nearly always absent
8. About 70 per cent of the cases of solitary kidney found with some other type of congenital malformation, particularly of the genital tract
9. Diagnosis obtained cystoscopically and pyelographically by the descending or ascending urographic method

#### HYPOPLASTIC KIDNEY

Unilateral renal hypoplasia is that condition in which a kidney that is apparently well developed anatomically and histologically is diminutive, fetal or infantile in size, or hypoplastic or defectively developed. While apparently having good secretory function in regard to elimination of urea and of color dye, the organ does not have enough capacity for undergoing functional hypertrophy to sustain life. Chopart,<sup>1</sup> Morgagni,<sup>2</sup> Cruveilhier,<sup>3</sup> Sappey,<sup>4</sup> Testut,<sup>5</sup> Rayer<sup>6</sup> and other earlier anatomists knew that one kidney might be large and the other small, but these observers did not differentiate congenital or primary hypoplasia from sclerotic, inflammatory and other forms of secondary contractions of atrophy. Indeed, the term atrophy, so frequently used in the literature, misleads in the conception and proper understanding of the condition, because these kidneys have at no time been larger than when found. Hence it is a condition of renal disparity, and many authors have described it as a rudimentary or infantile organ. There is an arrest in its development and not an atrophy. Gastaldi,<sup>7</sup> who reported sixty-six cases in his thesis, had the same idea, and termed it an inequality of renal volume, but did not differentiate the type of hypoplastic kidney from that of renal aplasia and total agenesis. Cadoré<sup>8</sup> and Gerard,<sup>9</sup> in classifying the congenital anomalies of the kidney, included "relative atrophy," obviously meaning abnormal smallness of one kidney, and applied the term "absolute atrophy" to a more

1. Chopart: *Traité des maladies des voies urinaires*, Paris, 1821.

2. Morgagni: *De sedibus et causis morborum*, Leyden, C. Haak, 1765. Letter XXXI, art. 25; XLVIII, art. 16.

3. Cruveilhier, Jean: *Traité d'anatomie pathologique*, Paris, J. B. Baillière et fils, 1849.

4. Sappey, M. P. C.: *Traité d'anatomie descriptive*, Paris, V. Masson, 1850.

5. Testut, Jean: *Tratado de anatomi humana*, Barcelona, Salvat y Ca, vol. 4, p. 478.

6. Rayer: *Traité des maladies des reins*, Paris, J. B. Baillière, 1841. See also his *Atlas*, 1837.

7. Gastaldi, M.: *Contribution à l'étude de l'inégalité du volume des reins et de l'atrophie congénitale unilatérale*, Thèse de Paris, 1910.

8. Cadoré, F. L.: *Les anomalies congénitales du rein chez l'homme*, Thèse de Lille, 1903, no. 144.

9. Gerard: *Les anomalies congénitales du rein*, J. de l'anat. et physiol. 41:241 and 411, 1905.

marked lesion. Teyssèdre,<sup>10</sup> in his thesis, used the term renal agenesis, and Polack<sup>11</sup> also described and classified the condition as agenesis, distinguishing a relative and an absolute type. In more recent literature, Albarran,<sup>12</sup> Marion,<sup>13</sup> Papin,<sup>14</sup> and Eisendrath and his co-workers<sup>15</sup> classified this condition more properly as hypoplasia, while McArthur,<sup>16</sup> Geraghty and Plaggemeyer<sup>17</sup> and other writers described it as the infantile kidney. Coplin<sup>18</sup> emphasized the condition of unilateral hypoplasia, explaining the possibilities of defective arteriogenesis in relation to the so-called hypogenetic nephritis. Astraldi<sup>19</sup> and Papin and Verliac<sup>20</sup> of the Necker Clinic also more recently stressed the congenital origin of this malformation as well as the concomitant anomalies of the genital tract, and reported a case in which the patent ureter of the hypoplastic kidney opened into a seminal vesicle.

However, the borderline between hypoplastic kidney and renal aplasia has not, on the whole, been well established, either clinically or histologically, since most of the pathologists include this recognized type of lesion under unilateral congenital or acquired atrophic kidney, as if it were due to an associated pathologic process. In 1902, Albarran<sup>12</sup> was among the first to call attention to the danger of this hypoplastic kidney, reporting a case in which, with good elimination of urea and of color dye, and apparently good concentration of the chemical

10. Teyssèdre, Emile: Contribution à l'étude des anomalies de développement du rein, Thèse de Paris, 1892, no. 370.

11. Polack, Lazare: Contribution à l'étude des agénésies rénales, Thèse de Bordeaux, 1909, no. 64.

12. Albarran, Joaquin: Exploration des fonctions des reins: Etude médico-chirurgicale, Paris, Masson et Cie, 1905.

13. Marion, G.: Traité d'urologie, Paris, Masson et Cie, 1928, p. 418; Hypoplasie rénale, discussion, Bull. Soc. franç. d'urol., séance du 17 mars, 1930, p. 50. Legueu: Hypoplasie rénale, discussion, Bull. Soc. franç. d'urol., séance du 17 février, 1930, p. 62. Chevassu: L'hypoplasie rénale, discussion, Bull. Soc. franç. d'urol., séance du 17 février, 1930, p. 62.

14. Papin, Edmond: Anomalies congénitales du rein, Encyclopédie française d'urologie, Paris, Doin et fils, 1914, vol. 3, p. 227. Verliac, Papin and Astraldi: L'hypoplasie rénale, Bull. Soc. franç. d'urol., Feb. 17, 1930, no. 2, p. 56.

15. Eisendrath, D. N., and Rolnick, H. C.: Textbook of Urology, ed. 2, Philadelphia, J. B. Lippincott Company, 1930, p. 575. Papin and Eisendrath: Les anomalies des reins et des urétères, Arch. d. mal. d. reins **2**:421, 1926.

16. McArthur, L. L.: Surg., Gynec. & Obst. **12**:391, 1911.

17. Geraghty, J. T., and Plaggemeyer, H. W.: The Practical Importance of Infantile Kidney in Renal Diagnosis, J. A. M. A. **61**:2224 (Dec. 20) 1913.

18. Coplin: Unilateral Renal Hypoplasia and Dysplasia, Am. J. M. Sc. **153**:381, 1917.

19. Astraldi, A.: Hypoplasie rénale congénitale, Arch. urol. de clin. de Necker **7**:47, 1931.

20. Papin and Verliac: Hypoplasie rénale congénitale avec aboutement de l'urètre dans la vésicule séminale, J. d'urol. **1**:431, 1920.

elements of the urine, he did a nephrectomy for renal tuberculosis, and eleven days later the patient died in a uremic coma. When the autopsy revealed a congenital hypoplastic or infantile type of kidney, he concluded that the hypoplastic kidney is incapable of undergoing compensatory hypertrophy after nephrectomy. Also, McArthur,<sup>16</sup> in 1911, reported another case in which he had performed a nephrectomy for tuberculous pyonephrosis, which was followed by death from renal insufficiency; at necropsy a tiny, infantile kidney, with normal parenchyma and normal secretion of urine, was found, but again the capacity for functional hypertrophy was lacking.

More recently, another author,<sup>21</sup> in a study on renal anomalies, reported an illustrative case of this type, in which, with good excretion of indigo carmine from both ureters and a positive pyelogram revealing an infected hydronephrosis, nephrectomy was done; four days later the patient had passed only 2 ounces of bloody urine and died with the typical symptoms of uremic poisoning; at autopsy, the left kidney was found to be of the hypoplastic type.

Geraghty and Plaggemeyer,<sup>17</sup> calling attention to the difficulty and importance of recognizing this so-called infantile kidney, reported on a study of 3,940 necropsies from the Johns Hopkins Hospital, among which they found 36 cases of atrophy from various causes; they stated that of these only 6 were unilateral, and that of the 6, only 3 belonged to the infantile or hypoplastic type; they further stated that there is much greater risk involved with a deficient kidney of the infantile type than with any other type of renal agenesis. All the statistics in this respect, therefore, are most confusing, because of the lack of differentiation and proper classification. In the future, however, these diminutive kidneys should be better known and properly recognized clinically, when careful routine urologic and urographic examinations are made.

The hypoplastic kidney, as a rule, is from three to six times smaller than the one of the opposite side, which is always hypertrophic. Two types may be described: In the first, the architecture of the renal parenchyma is normal with a normal pelvis and ureter, although the pelvis is of pear form or bottle shape and diminutive; the calices are also very small and sometimes unusually placed or anatomically disoriented. The second type is that in which the medullary portion and the pyramids are absent, and, therefore, there is only cortical substance and the pelvis may be of hydronephrotic type, as in Marion's case and in one of the cases that I am here reporting. In some of these cases the microscopic study reveals rudimentary glomeruli and tubules. In others the tissue resembles that of a normal kidney but is present in minimal amount. I am reporting two such cases that have been correctly diagnosed clinically and which were confirmed at operation, as

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21. Magoun, J. A. H.: Renal Anomalies, *J. Urol.* 27:435 (April) 1932.



can be seen in the report of the case. The chief diagnostic sign in hypoplastic kidney is marked decrease in function, both quantitatively and qualitatively, with reference to excretion of urea and elimination of color dye in comparison with that of the opposite side when the latter is normally and fully developed. But when the kidney of the opposite side is suffering from some type of associated pathologic process, the secretory function of both organs is affected and definitely diminished. Hence, the differentiation necessary to establish a correct diagnosis depends on the interpretation of the bilateral pyelogram combined with

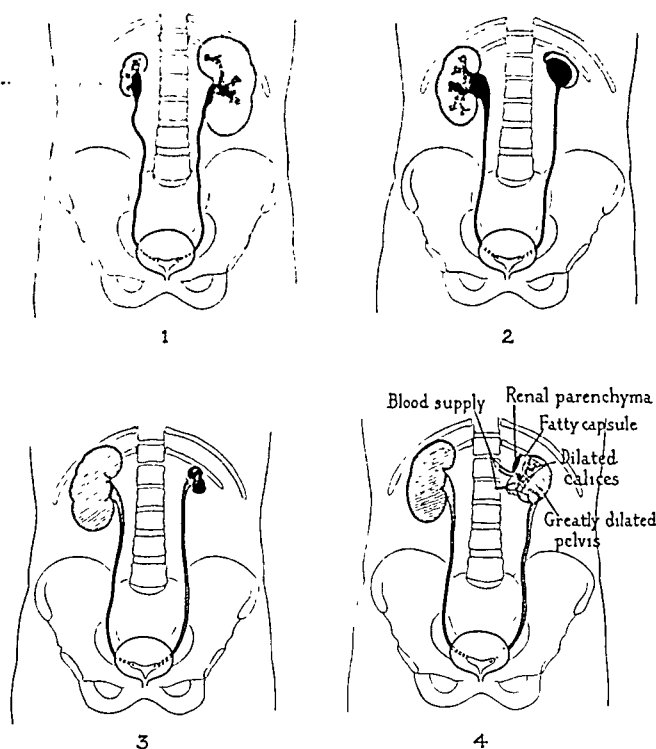


Fig. 1.—The different types of hypoplastic kidney, as collected from the literature: 1, author's case, representing a typical right hypoplastic kidney with marked hypertrophy of the left kidney; 2, a left hypoplastic kidney in which only cortical substance is present with no evidence of calices, papillae or pyramids; 3, a diminutive hypoplastic kidney with rudimentary pelvis and patent ureter; 4, marked hydronephrosis in an extremely hypoplastic kidney in which patency of the ureter and renal function are present. Note that in the hypoplastic kidney the ureter is always patent and there is evidence of some renal function.

the shadow cast and outline of the kidney obtained in a good x-ray plate, in which the size and position of both organs can be accurately made out. The pyelographic and roentgenographic evidence furnished by the outline of the kidney, which may be very small with extremely small pelvis and with calices absent or rudimentary, in contrast with hypertrophy of the opposite normal kidney, will serve to verify the diagnosis.

With this congenital malformation of hypoplastic kidney in mind, the advisability of taking a bilateral pyelogram in order to detect this condition is beyond all question. In the future, many of these cases may be clinically recognized through the facility with which the method of intravenous pyelography can be used. Nevertheless, in many of these cases, when the intravenous injection of iopax for the purpose of finding out the condition of the kidney is employed, and the opaque substance is not sufficiently concentrated or eliminated by the kidneys, and is therefore not well visualized, it will always be necessary, and perhaps safer, in order to establish a correct diagnosis, to use the ascending method of taking ureteropyelograms for the purpose of verifying a suspected condition and revealing the presence of a hypoplastic kidney.

#### REPORT OF CASES

##### CASE 1.—*Nephrectomy for hypoplastic kidney.*

Mrs. L. H., a housewife, aged 26, came to the Brady Urological Clinic of the New York Hospital on Oct. 31, 1930, complaining of pain in the right lumbar region with slight frequency of urination day and night, and also dysuria and pyuria. The pain in the lumbar region and upper right quadrant had been intermittent since she was 9 years of age. This pain lasted for four or five days and disappeared. She also had pain in the left lumbar region. Cystoscopy had been performed elsewhere and a diagnosis of pyelitis and pyelonephritis made, but no treatment had had any effect on her condition. The left kidney was enlarged and tender on palpation. The right kidney was not palpable, but there was pain in the right upper quadrant on deep palpation. Although well developed, the patient was of feeble constitution, but had a 6 year old child living and well. Aside from the fact that her menstrual history had always been painful and irregular, no other abnormalities were made out.

On November 3, cystoscopy was performed and both ureters were catheterized; a differential renal test revealed that function of the right kidney was much diminished in comparison with that of the left. The culture also revealed *Bacilli coli-communis* from the right ureter and bladder, while culture from the left was negative. Also, microscopic examination of the wet specimen revealed two white blood cells per field, while from the left side there was no pus.

On November 13, cystoscopy was again performed and bilateral pyelograms were taken. The roentgen report on the genito-urinary tract revealed that the shadow of the left kidney was considerably enlarged; and while the shadow of the right kidney was not clearly seen, there was no shadow indicative of stone anywhere in the urinary tract. The pyelogram of the right kidney revealed a small elongated bottle-shaped pelvis of infantile type, showing diminutive calices and some dilatation of the upper calices; also some distortion of the ureter was seen, and the impression was that of a hypoplastic organ which had not been fully developed (fig. 2). The pyelogram of the left kidney showed a slightly dilated pelvis with dilatation of the major and minor calices; it also revealed that the left kidney was about four times larger than the right, and that apparently this hypertrophic organ was carrying on in a compensatory manner the function of its mate. With this finding, cystoscopy was again performed on November 24, at which time the specimen collected from both sides was sent to the laboratory for inoculation into a guinea-pig in order to rule out the possibility of tuberculous infection. At the

same time, in the routine treatment, each kidney was irrigated with a solution of dextrose containing an acridine derivative and a bougie no. 8 was passed to each renal pelvis to dilate the ureters, to correct infection and to assure better drainage. To ascertain the differential function and to determine whether nephrectomy of the infantile organ was indicated, the functional test was repeated. One week later, December 1, when cystoscopy was again performed, the differential functional test was made.

The specimen of urine from the right ureter was bloody and contained 0.5 Gm. of urea per liter; that from the left ureter was clear and contained 4 Gm. of urea per liter.

The phenolsulphonphthalein test gave the following results: time of appearance from the right ureter, five minutes; per cent of phenolsulphonphthalein, 1.5; time of collecting, ten minutes; time of appearance from the left ureter, two minutes; per cent of phenolsulphonphthalein, 9; time of collecting, ten minutes.



Fig. 2 (case 1).—*A*, bilateral pyelo-ureterogram, revealing a typical picture of a right hypoplastic kidney with a very diminutive pelvis and a slight dilatation of the upper calix. There can also be seen the rudimentary lower and middle calices, and a faint shadow of the outline of the diminutive organ. *B*, pyelo-ureterogram of the left kidney from the same case, revealing an enormous kidney shadow with a normal pelvis as the expression of a compensatory functional hypertrophy. *C*, pyelogram of the specimen removed at operation, revealing the diminutive type of infantile hypoplastic kidney.

Microscopic examination of the sediment of the wet specimen from the right ureter showed 1 epithelial cell, 6 red blood cells and 2 white blood cells per high power field. The specimen from the left ureter showed 3 epithelial cells per high power field, much detritus and crystals.

Culture of urine from the right ureter showed *B. coli-communis*; the urine from the left ureter was normal, and that from the bladder contained *B. coli-communis*.

The conclusion was, therefore, that the patient was suffering from a faulty development of the right kidney, the so-called infantile kidney, having practically

no function and associated with pyelitis and pyelonephritis. In view of this, she was admitted to the hospital and nephrectomy was done under spinal anesthesia on Jan. 20, 1931.

I found at operation that the kidney was very easily exposed by the lumbar oblique incision, and that there was little perirenal fat present. On opening the fatty capsule, the kidney was found to be of infantile aspect and extremely small. The ureter was easily separated and ligated. The renal pedicle of the kidney, which was also seen to be very small or atrophic, was likewise easily dissected free from the surrounding tissues, clamped and tied, and the kidney was removed,

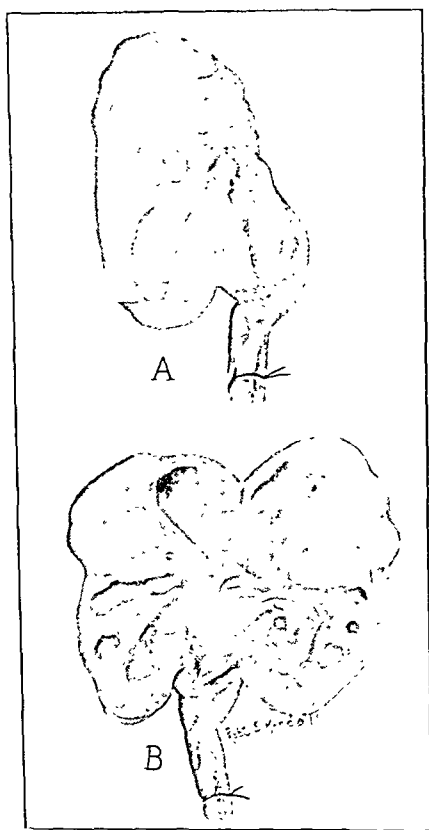


Fig. 3 (case 1).—Drawing of the specimen removed at operation: *A*, the anterior aspect of the diminutive kidney; *B*, sagittal view, laid open, of the infantile hypoplastic kidney, revealing slight dilatation of the upper calix and a slight degree of hydronephrosis. Note that the parenchyma of the kidney is composed of medullary and cortical substance, and also that the excretory apparatus is very diminutive and hence incapable of undergoing compensatory hypertrophy.

this constituting one of the simplest and easiest nephrectomies I have ever encountered. Recovery was uneventful, and the patient left the hospital in good condition two weeks later.

The specimen removed at operation revealed the presence of a hypoplastic type of kidney, associated with pyelitis and pyelonephritis. A pyelogram was made of the specimen removed at operation (fig. 2 *C*); it showed a small amount of renal

parenchyma and a tiny infantile type of pelvis, which obviously corresponded with the pyelogram taken before the operation, thus giving full evidence of the correctness of the diagnosis.

Macroscopically, the specimen was a diminutive or infantile organ with a slight degree of hydronephrosis (fig. 3). On cutting the specimen in half the medullary and cortical substances were found to be within normal limits. The architecture of the organ was also quite normal, except that it was diminutive in type and that some of the pyramids and calices as well as the papillae were distorted owing to the association of slight hydronephrosis with pyelitis and pyelonephritis. However, the ureter and ureteric-pelvic junction were within normal limits and truly patent.

The histologic report of the specimen was as follows: The specimen consisted of a kidney measuring 7 by 4 by 2.5 cm. The microscopic sections showed marked scarring of the cortex within large portions, disappearance of the glomeruli, dilatation or atrophy of the tubules, increased fibrous stroma and thickening of the arterioles with diminution of their lumina. The pelvic mucosa was heavily infiltrated by lymphocytes. The covering epithelium was not well preserved. In some of the thicker parts of the kidney more normal appearing glomeruli and tubules were seen, but even here there were streaks of scarring with varying stages of thickening of Bowman's capsule and fibrosis of glomeruli.

The conclusion to be drawn from this case is that the clinical evidence may be misleading for the diagnosis, since this hypoplastic or infantile type of kidney has a certain amount of function in regard to elimination of urea and color dye, and the chemical elements of the urine may be normal. But when anuria sets in, or nephrectomy is done for an associated pathologic process in its mate, this fetal type of kidney is incapable of undergoing hypertrophy. This therefore brings out the fact that in this diminutive type of pelvis the dynamism of the emptying time is affected in two ways: first, by the retention and lack of excretory elimination and, secondly, by the development of urinary stasis, which will ultimately lead to hydronephrosis, pyelitis and pyelonephritis. The diagnosis is made urographically, and two groups of cases must be considered: first, the type herein described of a hypoplastic organ with hypertrophy of its mate, when nephrectomy of the diminutive kidney is the proper indication, and, secondly, the type in which the hypertrophic organ is the one suffering from the associated pathologic process, while the infantile kidney of the opposite side is executing a certain amount of function but not enough to sustain life when left alone. In this case the hypertrophic kidney should be given the most careful treatment, such as one would accord in cases of a single kidney when conservative surgical and urologic therapy is the only proper indication.

This patient was examined just one year after her operation. She has gained in weight and is free at the present time from urinary symptoms. This case shows how these conditions can be accurately diagnosed today by the routine method of investigation, with both the differential renal functional test and the urographic data.

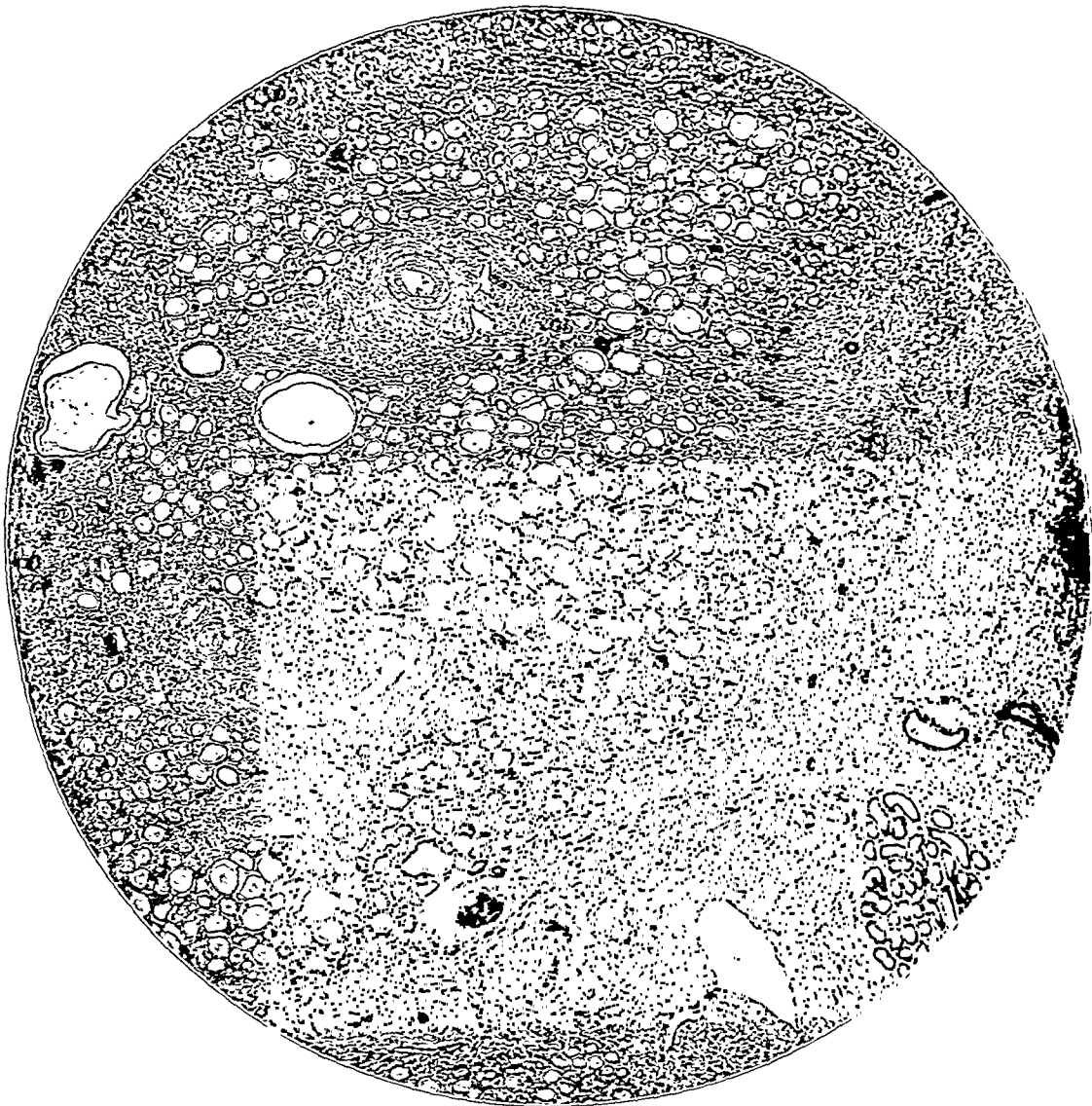


Fig. 4 (case 1).—Photomicrograph of section made from the removed specimen, revealing embryonic type of tubules, hyalinization of glomeruli and marked sclerosis of the blood vessels. Note the degeneration of tubules with flattening of the epithelium and dilatation of tubules and glomeruli to the extent of cyst formation. Also note here and there fibrosis of the connective tissue, the whole revealing the presence of a hypoplastic kidney.

CASE 2.—*Nephrectomy for hypoplastic kidney.*

J. L., a man, aged 21, had been complaining of indefinite abdominal pain and urinary disturbances at different intervals for more than ten years. Three years ago he was admitted to the surgical ward of the New York Hospital where an appendectomy was done. Nine months later he had an operation for undescended right testicle. His chief complaint, when admitted to the urological department of the New York Hospital on Sept. 19, 1930, was pain on the left side of the abdomen and in the region of the left kidney; he also complained of intermittent pain in the right lumbar region accompanied by frequency of urination, dysuria, pyuria and urgency, and marked burning on urination. The pain was more marked in the left lower quadrant in the region of the lower left ureter. He had been treated elsewhere for cystitis and cystoscopy had been done on several occasions, but no definite diagnosis had ever been made. Cystoscopy was performed at the



Fig. 5.— *A*, pyelo-ureterogram of the left side revealing an unusual shape of pelvis without calices and also a diverticulum of the lower portion of the ureter. *B*, pyelogram made in the same case after the injection of iopax, revealing good excretion of the opaque substance with presence of a slight hydronephrosis and good function of right kidney. Note the bizarre shape of pelvis on the opposite side, disclosing the presence of a congenital malformation of the left kidney, which was assumed to be a hypoplastic organ.

urological clinic of the New York Hospital on September 19; both ureters were catheterized, and a differential functional test made.

The specimen of urine from the right ureter was clear and contained 9 Gm. of urea per liter; that from the left ureter was also clear and contained 0.5 Gm. of urea per liter. The phenolsulphonphthalein test gave the following results: time of appearance from the right ureter, eight minutes; per cent of phenolsulphonphthalein, 3; time of collecting, ten minutes; from the left ureter, no phenolsulphonphthalein; time of collecting, ten minutes.

Microscopic examination of the sediment of the wet specimen from the right ureter showed 11 red blood cells and 18 epithelial cells per high power field; from

the left ureter, 18 white blood cells in clumps per high power field and many epithelial cells.

A roentgenogram and pyelogram of the left side showed a greatly distorted left kidney with complete absence of calices; also the ureterogram of the left side disclosed a diverticulum at the lower end and much distortion throughout. As there was practically no function on the left side, it was thought that the patient had either an atrophic or diminutive kidney on that side or possibly a tuberculous infection. Guinea-pig inoculation was done on several occasions, but no tuberculous infection was demonstrated. To check up these findings an intravenous injection of iopax was given, with the result that the right kidney was found to

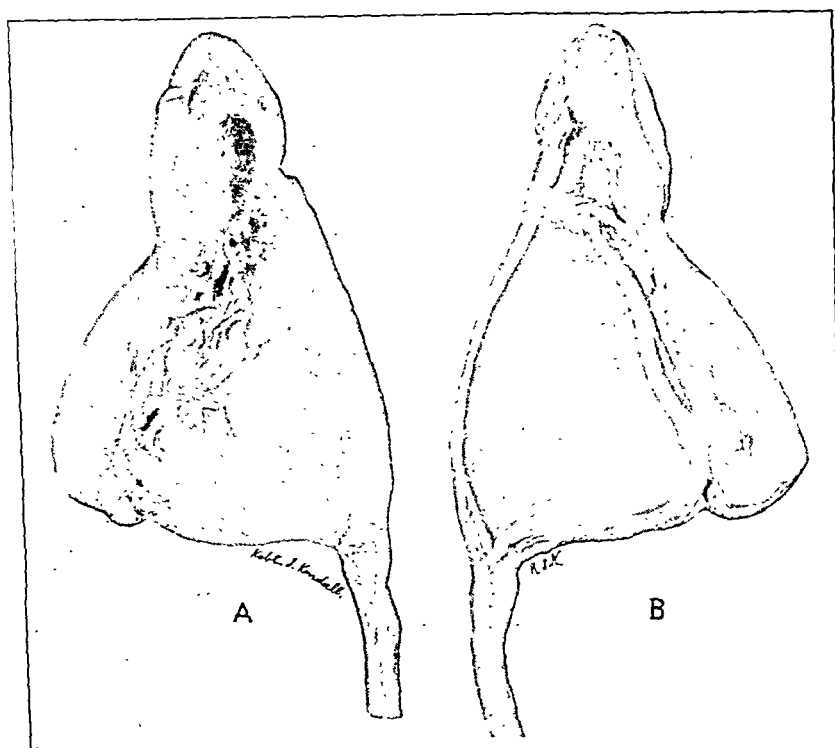


Fig. 6 (case 2).—*A*, drawing of the specimen removed at operation, showing evidence of an underdeveloped kidney with marked fetal lobulations and hydro-nephrotic plevis. *B*, sagittal view of the same, revealing that the renal parenchyma is here formed only of cortical substance and that there is no evidence of calices, papillae or medullary substance of the organ. This type of hypoplastic kidney, although having some excretory function, is incapable of undergoing compensatory hypertrophy and should be diagnosed by both the ascending and descending urographic methods.

have good excretion of the opaque substance, thus establishing the presence of a normal right kidney. In the left kidney, however, the elimination of the iopax did not appear for three hours, and the shadow thus obtained showed an irregular shape of the pelvis with absence of calices, thereby disclosing the presence of a pathologic or atrophic kidney, for which nephrectomy was recommended.



The operation was carried out on September 26. When the kidney was removed at operation, it was found to be infantile in type with a hydronephrotic pelvis and little cortex. When the organ was opened, it could readily be seen that it was formed only of cortical substance, that there were no pyramids, papillae or calices and that the thin and narrow margin of the cortical substance was attached to a hydronephrotic pelvis, as can be seen in the drawing here reproduced. The patient made an uneventful recovery, leaving the hospital eighteen days after the operation. But owing to the diverticulum left behind after an incomplete nephroureterectomy, he is at present complaining of some discomfort, for which he has been receiving cystoscopic treatments. He has been advised to have a secondary ureterectomy for the removal of the infected stump of the ureter and the diverticulum. The conclusion to be drawn from this case is that the presence of a congenital malformation of the kidney had been the underlying cause of the pathologic process, and that the organ was a hypoplastic kidney with practically no excretory renal function and, therefore, incapacitated to undergo compensatory hypertrophy in order to sustain life.

Examination of the specimen showed a kidney measuring about 9 cm. in length, with a width varying from 2 cm. at the upper pole to 6 cm. at the lower pole and 4 cm. in thickness. The organ was irregular in shape with remnants of the fetal lobulation. On opening the kidney, it was evident that the pelvis was greatly dilated, measuring about 3 cm. in width, and that it extended through the whole length of the kidney, like a thick-walled sac. Only the remnants of the calices could be seen; the pyramids were flattened out. Microscopic sections showed tubules which were on the whole quite well preserved. There was slight congestion of the vessels, including the capillaries of the glomeruli. A few of the tubules and capsular spaces contained a pink staining of homogeneous material. The epithelium of the pelvic mucosa was well preserved. The underlying fibrous tissue was increased in amount and contained a diffuse scattering of lymphocytes and a few plasma cells. The ureter showed some increase of fibrous tissue beneath its lining of epithelium, and also a diffuse infiltration of lymphocytes.

The final diagnosis was a hypoplastic kidney showing marked extrarenal pelvis, with chronic pyelitis and practical absence of pyramidal tissue.

The report of these two illustrative cases of hypoplastic kidney will serve to attract attention to this unique condition of the kidneys, in which the organ, when infantile or hypoplastic in type, owing to underdevelopment, is incapacitated for undergoing compensatory hypertrophy or for functioning efficiently enough to sustain life. It is essential that the surgeon be well acquainted with the clinical importance of this entity and be able to recognize it, in order to prevent fatal results. Today the diagnosis of this clinical condition is possible if based on the differential functional renal test and on the comparative study of pyelographic data, as the report of these two cases has demonstrated. It is very important, therefore, that the differential urographic diagnosis of the condition be borne in mind, since this abnormal type of kidney may readily be confused with the presence or the association of other different types of lesions, such as are frequently observed in the acquired or secondary atrophy of one kidney, due to tuberculosis, tumor, calculous diseases, pyelonephritis or hydronephrosis. These acquired types of pathologic process in the kidney are seen commonly at postmortem examination

and also on pathologic or clinical examination of cases. Furthermore, the hypoplastic kidney should always be differentiated from other common types of anomalies, such, for instance, as the double kidney, in which the appearance in the pyelogram of the upper pelvis alone, always

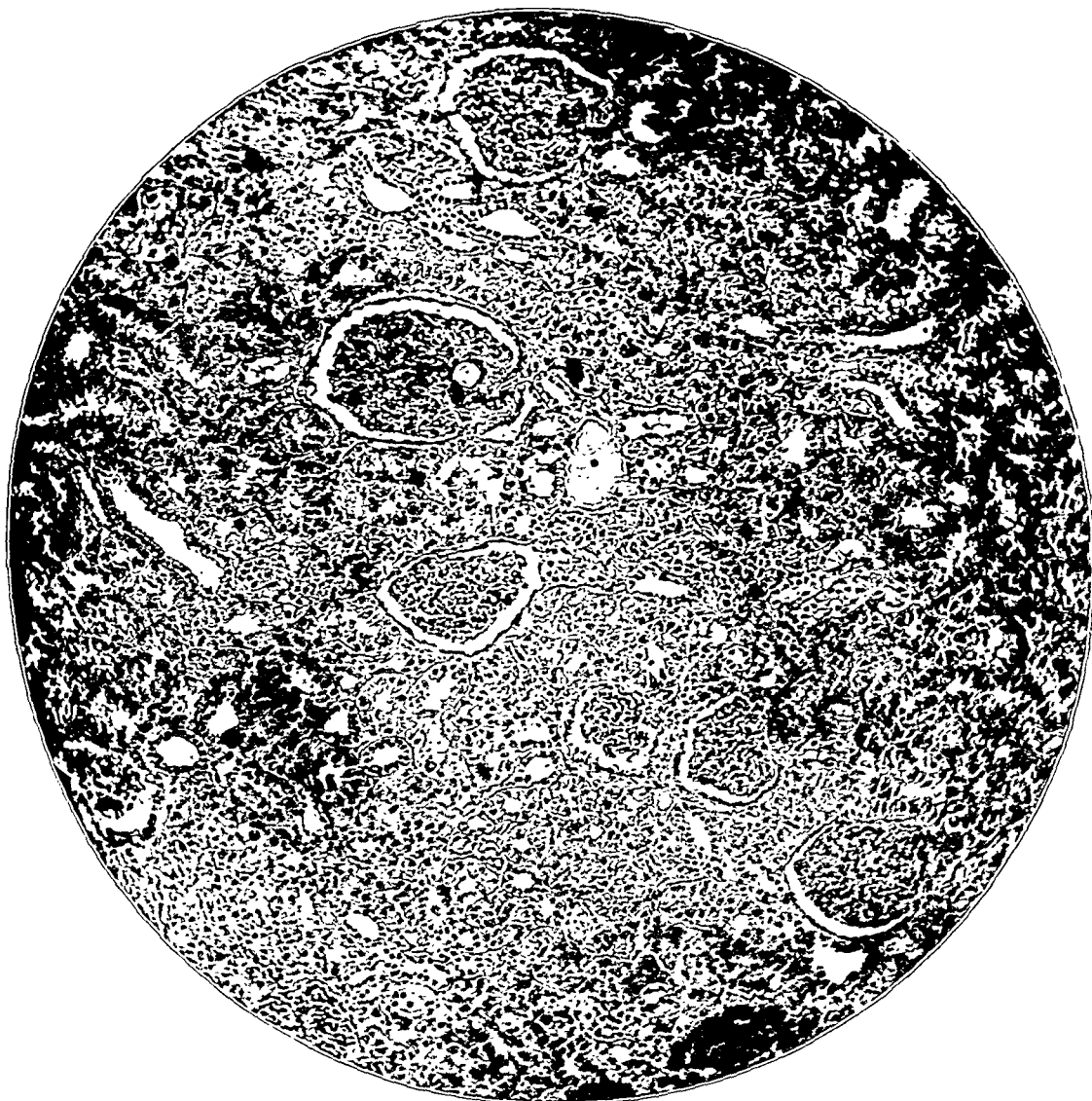


Fig. 7 (case 2).—Photomicrograph of section made from the removed specimen, in which the histologic studies reveal the presence of glomeruli and tubules of a normal kidney tissue, although the clinical appearance and the gross anatomopathologic data are obviously those of a hypoplastic kidney.

diminutive in size and assuming a T form or mushroom shape, causes a misleading interpretation of the urographic findings, if, in taking the

ureteropyelograms, the double pelvis and ureters have not both been properly visualized. This error is not infrequent when cystoscopy has been done by inexperienced hands, and is usually due to improper identification of the two ureteral orifices on the one side of the bladder or to failure to take the routine ureteropyelograms in cases in which the two ureters of the double kidney pelvis unite before reaching the bladder. A number of such cases have been seen in the clinic. Nowadays these could be easily checked up by the intravenous method of urography. Hence, these so-called rare anomalies of the upper urinary tract should be carefully looked for and identified by means of both urographic methods of taking urograms, since a diminutive or rudimentary pelvis

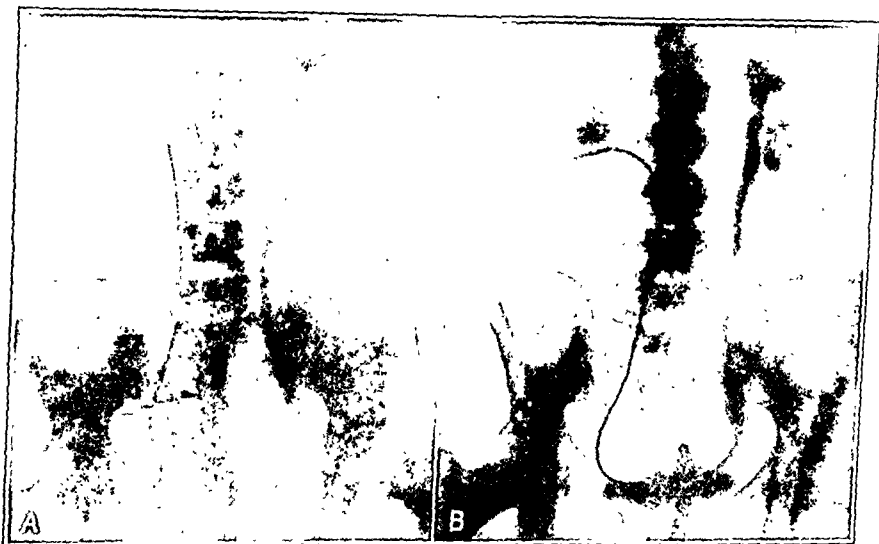


Fig. 8.—*A*, pyelo-ureterogram of the left kidney revealing a diminutive size of renal pelvis, resembling that of a hypoplastic kidney, when in reality such a T-shaped or mushroom-shaped pelvis indicates the presence of the upper pelvis of a double kidney. *B*, the two ureters of the same double kidney have been injected with the opaque substance and the pyelo-ureterogram shows the anomaly of a double kidney with double pelvises and double ureters on the same side.

seen in a retrograde pyelogram is not always conclusive evidence of a hypoplastic kidney.

Finally, these three types of renal lesions under discussion have another generic relation or clinical similarity which it may be of interest to mention: namely, that the hypertrophic kidney, which is anatomically larger since physiologically it is carrying on the function of its mate, is commonly associated with nephritis and pyelonephritis, and consequently is always symptomatically painful. Both organs may, therefore, be affected at the same time with some other types of associated pathologic process. Hence, in this series of cases, it has been observed that the presence of persistent pain in both lumbar regions may mislead

at the outset in the clinical interpretation. Lumbar or abdominal pain on the one side is due to the pathologic position occupied by the hypertrophic and hyperfunctionating kidney, while on the other side it is usually caused by the hypoplastic or aplastic condition, in which, because of the lack of function and the chronic infection, the retained urine and the lack of dynamism cause renal nephralgia in the corresponding lumbar and abdominal regions. These clinicopathologic factors must, therefore, be borne in mind, since a hasty examination of a patient with a large palpable kidney on the one side might lead to a fatal operation, if the necessity for a differential renal functional test or pyelographic studies was not recognized.

Although a thorough examination and careful history are always important in the clinical study of any given case, the differential diagnosis in potential surgical anomalies or any other conditions of the kidney should always be based on the comparative estimation of the renal functional test and on the evidence obtained from the cystoscopic, roentgenographic and urographic data. In this way alone can a sound and permanent prognosis be assured.

#### RENAL APLASIA

The condition of unilateral renal aplasia may be best explained by saying that it is the extreme expression, in a clinical and anatomopathologic sense, of hypoplasia of the kidney, which is characterized by a congenital defect or arrest of development of one kidney, accompanied by hypertrophy of its mate. It is, however, differentiated from hypoplastic kidney in that the rudimentary and diminutive structure, supposed to be a renal organ, is a small mass of aberrant fibrous tissue, which, although it may be microscopically formed of embryonic and sclerotic or even calcified glomeruli and tubules, has at no time had any excretory function. Moreover, the excretory apparatus per se of pelvis, calices and ureter is absent or incompletely developed.

In the study of renal aplasia two types must be considered from a clinico-anatomopathologic standpoint.

First, there are those cases in which the fibrous mass of renal tissue, which may be found in the renal fossa or its vicinity, covered by the pararenal fatty capsule of the lumbar region, has a small or diminutive underdeveloped renal artery, which runs from the aorta to the aberrant amorphous mass of renal fibrotic tissue.

There is no evidence, however, of true renal pedicle, renal pelvis or patent ureter, although a short, rudimentary, incomplete and functionless ureter may always be discovered in the course of a careful post-mortem examination. It is thus on the whole an organ which definitely has never shown any signs of existence in a true sense, or ever accomplished any anatomic or physiologic function. Nevertheless, because

of the presence of a diminutive renal artery, assuring a direct blood supply, it can eliminate into the mass of tissue the intravenously injected opaque substance, bringing out by the roentgenogram the surprising revelation of the presence of aberrant renal tissue and thus serving to establish a diagnosis.

The second group of cases of renal aplasia consists of those in which there is no evidence of a renal artery in the diminutive aberrant fibrous mass of connective tissue, and, therefore, no direct blood supply from the aorta or iliac arteries. All that exists is collateral branches coming from the suprarenals and surrounding tissues, so that no substance opaque to the roentgenograms can be eliminated to produce any shadow cast for diagnostic purposes. Furthermore, the pelvis and upper portion of the ureter are anatomically or histologically absent, but nevertheless there is always evidence of the remnant of a function-

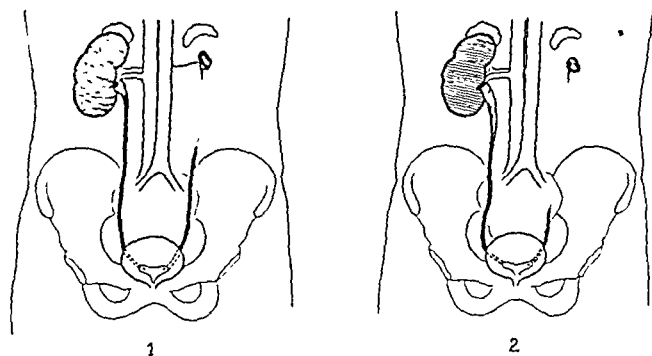


Fig. 9.—Drawing to illustrate the two types of renal aplasia found in the literature: In 1 is shown the instance in which the aplastic rudimentary renal organ has a direct blood supply from the aorta by means of a diminutive renal artery. Note that there is no evidence of renal pelvis and that the ureter is underdeveloped and hence not patent. In 2 is shown the instance in which an aberrant, aplastic fibrous mass of renal tissue is found in the vicinity of the renal fossa, without direct blood supply from the aorta. Note the rudimentary development of the functionless ureter on the aplastic side and also the presence of both suprarenals.

less and incomplete or obliterated ureter in the aplastic side of the urinary bladder.

These two types of renal aplasia are the ones that I have been able to find in the misleading and confused literature of the report of cases, many of which have been recorded as congenital absence of one kidney when it is obvious that they were in reality instances of renal aplasia.

This rare condition of the undeveloped aplastic kidney has been observed occasionally at postmortem examination. Campbell<sup>22</sup> recently reported 39 cases from a series of 13,000 autopsies at Bellevue Hospital

22. Campbell, M. F.: Congenital Absence of One Kidney: Unilateral Renal Agenesis, *Ann. Surg.* 88:1039, 1928; personal communication to the author.

and claims that renal aplasia is found four times more frequently than congenital absence of a kidney. This assertion is also confirmed by other authors, whose findings from postmortem examination and anatomopathologic studies have been reported in the literature (Schilling,<sup>23</sup> Risel,<sup>24</sup> Lorenz,<sup>25</sup> Pfeiffer,<sup>26</sup> Ballowitz,<sup>27</sup> Heilbronn,<sup>28</sup> Gruber and Bing,<sup>29</sup> Rosenbaum<sup>30</sup> and others). This condition has seldom, however, been discovered at operation, unless a previous cystoscopic and urographic investigation has revealed it, as in MacKenzie and Hawthorne's cases published in 1928.<sup>31</sup> But in reality, not until the present time, with the advent of pyelography following intravenous injection, has the accurate clinical diagnosis of renal aplasia ever been possible in the history of medical science.

The clinical and surgical aspect of this condition merits careful scrutiny, since the aplastic kidney has no eliminatory function. Surgical therapy must, therefore, continue to be along very conservative lines, particularly when a radical operation such as nephrectomy is contemplated.

Renal aplasia must, moreover, be differentiated from secondary or acquired renal atrophy, particularly in cases of occlusion or autonephrectomy due to disease or an associated pathologic process such as is commonly observed both clinically and at postmortem examination. The varieties of renal atrophy are readily seen in chronic inflammatory lesions of the kidney, in traumatisms, tuberculosis, hydronephrosis, pyonephrosis, nephro-ureterolithiasis and other acquired lesions in which the kidney may undergo complete destruction or atrophy.<sup>32</sup> These instances of associated pathologic process may be conceded to be the cause of the acquired or secondary type of renal atrophy, which does

23. Schilling, F.: Ein Fall von hochgradiger Aplasie der Nieren, *Virchows Arch. f. path. Anat.* **232**:176, 1921.

24. Risel, Hans: Ueber Nierenhypoplasie, Freiburg, Speyer & Kaerner, 1903.

25. Lorenz, F. H.: Hypoplasie und Aplasie der Niere, München, Kastner & Callwey, 1907.

26. Pfeiffer, E.: Die Nierenhypoplasie, *Ztschr. f. urol. Chir.* **16**:193, 1924; **23**:332, 1927.

27. Ballowitz, E.: Ueber angeborenen einseitigen vollkommenen Nierenmangel, *Virchows Arch. f. path. Anat.* **141**:309, 1895.

28. Heilbronn, Joseph: Ueber congenitale Nierenanomalien, Würzburg, Stahel, 1902.

29. Gruber, G. B., and Bing, Leo: Ueber Nierenmangel, Nierenkleinheit, Nierenvergrößerung und Nierenvermehrung, *Ztschr. f. urol. Chir.* **7**:259, 1921.

30. Rosenbaum, R.: Ueber doppelseitige Nierenaplasie, Frankfurt. *Ztschr. f. Path.* **41**:136, 1931.

31. MacKenzie, D. W., and Hawthorne, A. B.: Unilateral Renal Aplasia, *Surg., Gynec. & Obst.* **46**:42 (Jan.) 1928.

32. Gutierrez, R.: The Value of Indwelling Ureteral Catheters in Urinary Surgery, *Surg., Gynec. & Obst.* **50**:441 (Feb.) 1930; Indications and Technic of Combined Ureteronephrectomy, *Ann. Surg.* **93**:511 (Feb.) 1931.

not need to be emphasized at this time, because it is obviously well understood both clinically and by animal experimentation (Albarran,<sup>33</sup> Beer,<sup>34</sup> Hinman,<sup>35</sup> and Barney<sup>36</sup>).

In essential renal aplasia, which is an arrest in its development, the true kidney has never been formed. It has also been observed that there is no associated pathologic process or concomitant primary lesion except the sclerosis of the embryonic tissues, and that there is no sound explanation for the absence of the cortical, medullary and excretory renal parenchyma, other than the conception that it is the result of a lack of development during intra-uterine life, in which the mesonephros by an aplastic process has not formed or produced the definitive kidney. Hence it is to be assumed that the remnants of an aplastic renal tissue are due to the remains of the primitive nephrogenic tissue, which have been left behind through an arrest in its development. Furthermore, this assertion can be substantiated to a certain extent by the recent work of Bagg<sup>37</sup> on congenital defects in mice, in which there have been observed roentgenographically many instances of absence of a kidney and other malformations, such as the development of rudimentary and diminutive aplastic and hypoplastic kidneys.

Renal aplasia must also be differentiated from congenital absence of one kidney in which there is no anatomopathologic evidence of a diminutive organ or even vestigial, aberrant tissue, so that neither the hypoplastic nor the aplastic kidney is in existence. In order to get rid of the confusion that reigns in this field, in which many authors have reported cases of congenital absence of one kidney when in reality there was evidence of renal aplasia, or vice versa, it appeared to me that it would be useful to work out a clinicopathologic classification that would make possible the differential diagnosis between these three conditions. To this end, I have summarized the most important clinico-anatomopathologic points of distinction, in the classifications which can be seen in the introduction of this communication.

It is obvious that the fallacies of renal aplasia are the clue to errors in diagnosis, which sometimes lead to fatal consequences even when urologic examination has been carried out. Clinically, the patient has no symptoms related to the urinary tract, and merely complains of pain

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33. Albarran, J.: *Etude sur le rein des urinaires*, Thèse Paris, 1889, no. 125.

34. Beer, Edwin: *Collected Papers*, New York, Paul B. Hoeber, Inc., 1931, p. 234; *Experimental Study of the Effects of Ureteral Obstruction on Kidney Function and Structure*, *Am. J. M. Sc.* **143**:885 (June) 1912.

35. Hinman, F., and Morison, D. M.: *Experimental Hydronephrosis*, *Surg., Gynec. & Obst.* **42**:209 (Feb.) 1926.

36. Barney, J. D.: *The Effects of Ureteral Ligation: Experimental and Clinical*, *Surg., Gynec. & Obst.* **15**:290, 1912. Papin, E.: *Les hydronéphroses, anatomie et pathogénie*, avec un atlas, Paris, Doin et Cie, 1930.

37. Bagg: *Am. J. Anat.* **36**:275, 1925.

in the lumbar region; on cystoscopy the bladder appears, as a rule, to be normal, and there can be seen two normally placed ureteral orifices, although the ureter on the aplastic side is always obliterated and is therefore without excretory function. It can, however, be probed and admits a catheter no. 5 or no. 6 French for a distance of 4, 5 or 6 cm., but the remaining vesical portion of the aplastic ureter has never in any instance any physiologic function. The blind stump has no connection with the fatty mass of sclerotic renal tissue; consequently, since the pelvis of the kidney appears never to have been anatomically and physiologically formed, there is no excretion of urine. The ureter accordingly may be absent or partially absent, or may be found as a

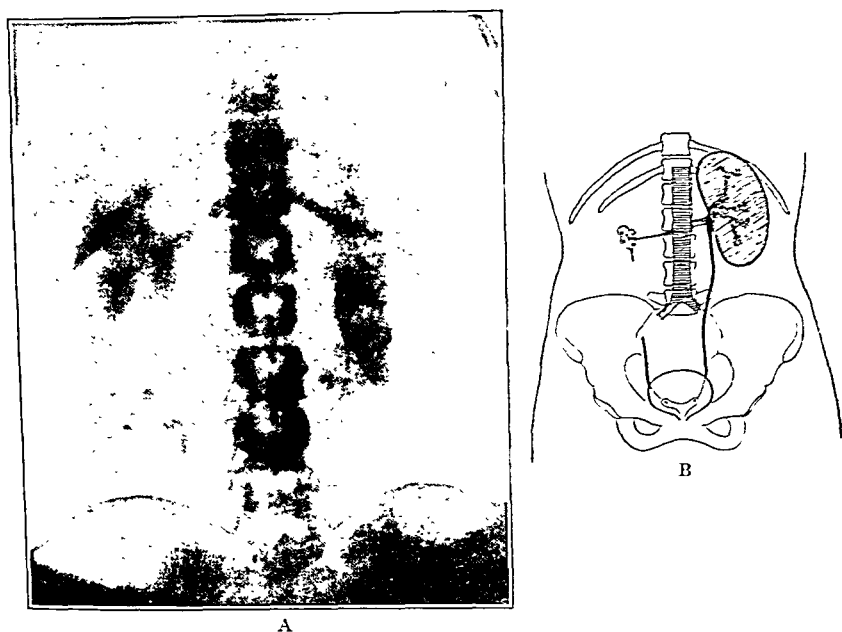


Fig. 10 (case 3).—Pyelogram in a case of renal aplasia following injection of iopax: *A*, the opaque substance has been eliminated with good concentration by the left kidney, revealing a normal pelvis and a hypertrophic left kidney. On the right side can be seen no outline of a kidney, but four faint shadows are cast by the roentgenogram, indicating that the opaque substance has been excreted by some renal substance, which served to establish a diagnosis of right renal aplasia. *B*, a drawing of the foregoing findings, which were confirmed at operation.

thin thread of fibrous tissue, closely adherent to the parietal layer of the lumbopelvic peritoneum and without clinical or pathologic significance. Furthermore, it can be observed clinically that when an opaque medium is injected into the catheterized aplastic ureter without excretory function, for the purpose of taking a pyelo-ureterogram, the ureter forces the fluid to regurgitate back into the bladder and does not allow it to go up the lumen. Thus no further investigation can be pursued, and only a hypothetic diagnosis is possible.



The blood supply is of extreme interest, since it may give the clue to the clinical or anatomopathologic diagnosis. At postmortem examination no kidney pedicle is ever found except a very elementary or rudimentary renal artery that may run from the aorta to this indefinitely fatty-renal, fibrous mass of tissue. Sometimes it is not possible to identify or find evidence of a true renal artery, and only the renal sclerotic mass of lipomatous tissue is observed, surrounded by innumerable aberrant blood vessels, which are collateral branches or anastomoses from the blood supply of the suprarenals. As a rule, there is no pelvis or ureter, but there may be found in the renal fossa, surrounded by a fatty capsule and bound down by fibrous bands of adhesions to the suprarenal, a small mass of fibrous tissue, formed by two or three small cysts attached together, representing dilatations of the renal tubules and apparently containing a few drops of yellow viscous fluid that may have the chemical characteristics of urine, as in MacKenzie's case and in the two cases that I am here reporting. This is why in taking a pyelogram following intravenous injection of any of the new drugs in use, a few tiny patches of shadow may be seen in the x-ray films, as in case 3 (fig. 10), in which the intravenous injection of iopax established the final diagnosis, which was suspected cystoscopically and confirmed at operation.

In the second case of renal aplasia here reported, the diagnosis was made at postmortem examination (see report of case 4) and the photograph of the specimen removed at autopsy plainly reveals all the characteristics of renal aplasia with its corresponding enlargement of the suprarenal gland (fig. 13).

The anatomopathologic characteristic in these cases of renal aplasia is that the histologic section of the specimen removed reveals, besides the anatomic features already described, the definite presence of renal tissue, characterized by embryonic or sclerotic tubules and glomeruli.

Sometimes the malpighian bodies may be occupied by deposits of lime or even calcification, and the elements of Bowman's capsule may undergo degeneration; there is also evidence of thick sclerosis of the blood vessels and connective tissue. The glomeruli have been invaded by connective tissue which appears to be undergoing hyaline degeneration. The matrix of this connective tissue is much degenerated and is formed of flattened epithelium; at some points there can be seen areas of calcification or complete sclerosis of the glomeruli, and sometimes dilatations and degenerations of the tubules to the extent of cyst formation, as in the instance of an underdeveloped polycystic kidney. Also, it is evident that the tubules may be found in groups and may appear very diminutive even under a high powered microscope. However, the problem of the histologic differentiation of renal aplasia from hypoplastic kidney and renal atrophy is almost incapable of solution by

microscopic studies alone, without taking into consideration the anatomo-clinicopathologic data already mentioned.

The symptomatology in renal aplasia, as in hypoplasia, is misleading, because these patients complain of pain in both sides of the abdomen. In the aplastic side this is due to the remnant of kidney tissue present; this acts as a foreign body, by virtue of the weight and irritant action of the amorphous renal mass, in which some of the glomeruli and tubules degenerate into cystic dilatations, which incarcerate a few drops

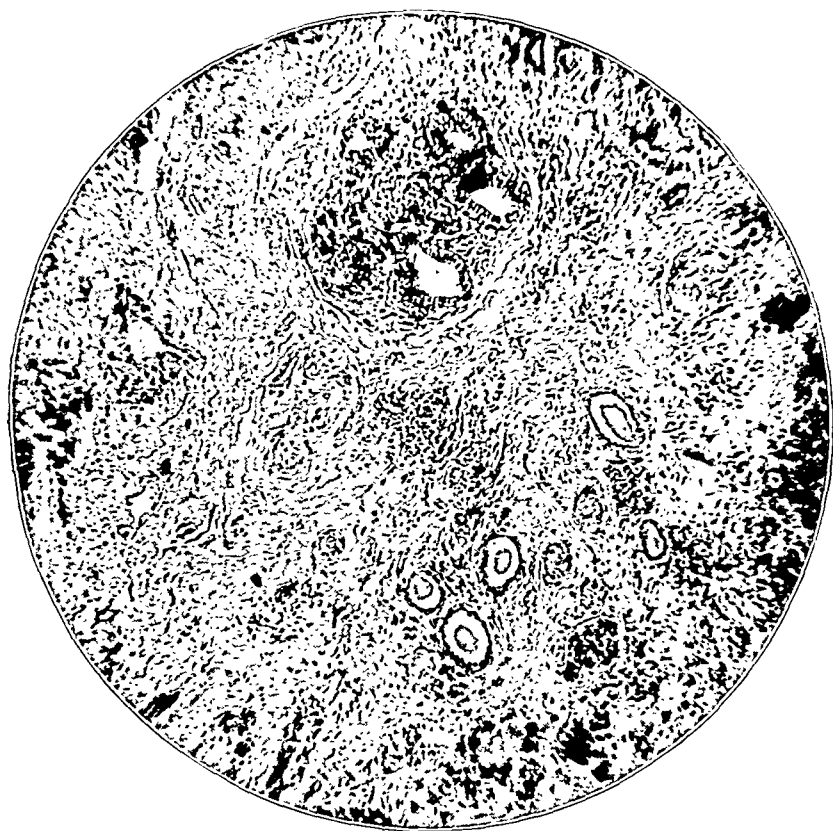


Fig. 11 (case 3).—Photomicrograph of a histologic section from a specimen removed at operation, revealing the presence of elements of renal tissue, and thus confirming the presence of an aplastic renal organ. Note that the histologic studies disclose the presence of rudimentary and also of dilated tubules with marked sclerosis of connective tissue, thickening of the blood vessels and calcification of the glomeruli.

of urine and ultimately, for lack of drainage, tend to form calcifications, and also to produce pressure on the surrounding tissues, thereby causing reflex symptoms and indefinite abdominal pain. In the other side, the pain is caused by the excessive size of its mate, which is anatomically and physiologically enlarged and overworked, resulting in compensatory

functional hypertrophy and, therefore, leading to painful symptoms here also. This bilaterality of symptoms must always be borne in mind in establishing the diagnosis.

The treatment of renal aplasia, whenever it is diagnosed, is surgical. It consists of the removal of the remnants of the aplastic functionless kidney with as much as possible of the pararenal fatty capsule.

The two illustrative cases of renal aplasia that I am reporting for the purpose of placing them on record are as follows:

*CASE 3.—Exploratory lumbo-abdominal operation in case of renal aplasia diagnosed previous to the operation.*

M. S., a housewife, aged 32, was admitted to the second surgical division of the New York Hospital, Nov. 2, 1931, and the case is here reported by courtesy of the director of the service, Dr. E. H. Pool, and the attending surgeon, Dr. S. Erdman. The chief complaint was pain in the right lumbar quadrant of over two years' duration. The patient had been examined elsewhere, and her condition was diagnosed as colitis, cholelithiasis, stone in the kidney or chronic appendicitis. She had slight frequency and nocturia but never recalled having had hematuria or pyuria. There was no history of trauma or of any operation performed previous to admission.

On physical examination, she was seen to be a rather obese widow of 32, looking in no way acutely or chronically ill. The kidneys were not palpable, and no mass or abdominal distention was made out. There was no tenderness, but just to the left of the umbilicus a dull pain was present, radiating toward the right lumbar region.

After the routine general laboratory and roentgen examinations of the gall-bladder and gastro-intestinal tract, the patient was sent to the urological department for examination. On cystoscopy, the interior of the bladder was found to be normal except for a slight congestion around the right ureteral orifice. The left ureteral orifice was normal in size, shape and position. Both ureters were catheterized. A no. 6 French catheter met an obstruction in the right ureter about 5 cm. from the bladder. On the left side, the catheter was passed to the pelvis of the left kidney without obstruction. A specimen was collected from the left kidney for culture, urea and microscopic examination, but no specimen could be collected from the right side. One cubic centimeter of phenolsulphonphthalein was injected intravenously and appeared in three minutes from the left side. No specimen or color dye could be obtained from the right ureter. X-ray pictures and a pyelogram were taken. The roentgenogram revealed no shadow indicative of stone anywhere in the urinary tract, but the outline of the left kidney was enlarged and could be definitely made out, while on the right side no renal shadow or outline of the kidney could be seen, and the sodium iodide injected into the right ureter regurgitated back into the bladder. Hence no pyelogram could be obtained on the right side. In view of this finding, a pyelogram after intravenous injection of iopax was advised. After various plates were taken, the outline of the pelvis of the left kidney was clearly made out; the plate revealed good excretory function with the presence of a normal pelvis, and apparently an enlarged hypertrophic kidney. In contrast to this, on the right side, no outline of any kidney could be seen, but four tiny indefinite shadows, each about the size of a pea, appeared at the level of the third and fourth lumbar vertebrae in the region of the renal area, giving a definite impression that the iopax had been excreted by some kidney substance. No definite evidence of pelvis or kidney could be made out. However, in view of the unusual

shadow brought out by the intravenous injection of iopax, associated with complete absence of renal function and impatency of the same corresponding right ureter, it was concluded that the patient should be submitted to an exploratory operation. It was assumed that a pathologic condition of the right kidney, possibly of congenital origin as in renal aplasia, was being dealt with. At operation a right lumbar oblique incision was made, and the fatty capsule opened, but no kidney was found. Instead, the operation revealed a small irregular, fatty, fibrous mass, which was clamped, tied and removed. The small shapeless mass of fibrous renal tissue was surrounded by blood vessels and bound down by adhesions, but no evidence of pelvis or ureter was identified or made out. The peritoneum was deliberately opened through the same lumbar incision, in order to explore the abdominal cavity, and on palpation the gallbladder and appendix were found to be normal. Moreover, an extensive exploration into the right lumbar region and down to the iliac fossa failed to reveal the presence of anything resembling a kidney. The posterior side of the peritoneum was also examined, for evidence of a possible ureter, but none could be traced or identified. Accordingly, the peritoneum was closed by a continuous suture and the exploratory operation was finished in the usual manner, closing the wound in layers without drainage. An uneventful convalescence followed, and the patient was discharged twelve days later in an improved condition. The pathologic report of the specimen removed at operation showed the presence of distorted, aberrant, renal tissue with sclerosis of the blood vessels, cyst formation and areas of calcification, as can be seen in the photomicrograph (fig. 11).

This case is perhaps the first to be put on record in which the diagnosis of renal aplasia was made urographically by the excretion of iopax administered intravenously. It may be concluded that in future cases of renal aplasia or other congenital malformations of the kidney, when accompanied by a small or rudimentary renal artery, pyelograms made following intravenous injection of iopax will serve to confirm and clarify the diagnosis, which in this case was hypothetically made by cystoscopy and retrograde pyelography.

*CASE 4.—Nephrectomy for multiple cortical abscess in a case of unilateral renal aplasia.*

Mrs. M. K., aged 30, a housewife, was admitted to the surgical ward of the New York Hospital on Dec. 16, 1915, and the case is here reported by courtesy of the director of that service, Dr. Eugene H. Pool. The chief complaint was pain in the right lower quadrant with vomiting and nausea. The patient had been acutely ill for two days previous to admission. Except for a persistent dull pain in the right lower quadrant during the last year, the past history was irrelevant.

On physical examination, the abdomen was rather large and rigid, making the palpation of deep organs almost impossible. Urinalysis showed a heavy, cloudy urine, and the eighteen hour specimen was 390 cc.; specific gravity, 1.013; reaction, acid; color, amber with presence of albumin and many epithelial cells; red and white blood cells were also present. In view of this finding, an x-ray picture was taken to rule out the possibility of urinary calculi. Cystoscopy was advised, but was not done, because the patient was menstruating, and moreover, her critical condition did not warrant delay. In view of the tenderness on the right flank, the palpable mass in the region of the appendix, the acute symptoms and the negative x-ray findings, the surgeon thought it advisable to explore the region of the appendix and gallbladder. Accordingly, on December 17, under general anesthesia, a

short right rectus incision was made, which established that the appendix and gallbladder were normal and that the mass was positively a kidney condition. The midline incision was then closed by layers, and the patient turned over into position for kidney operation. An oblique lumbar incision was made to expose the kidney, which was found to be large and to be surrounded by inflammatory adhesions of the perirenal fat and other structures. The surgeon's idea was only to drain the abscess of the kidney, on account of the extremely grave condition of the patient, since, as cystoscopy had not been performed, it was, of course, not known whether or not there was another functioning kidney on the other side. A nephrotomy was accordingly done in order to drain the multiple cortical abscess, but so much hemorrhage resulted that it became necessary to clamp the pedicle and perform a rapid nephrectomy in order to stop the profuse bleeding. The wound was closed, and the patient returned to the ward in poor condition. Five days later, as she was not eliminating any urine and was in a grave uremic condition, another operation was performed on the opposite side under general anesthesia in order to explore the condition of the left kidney. To the surgeon's surprise no left kidney

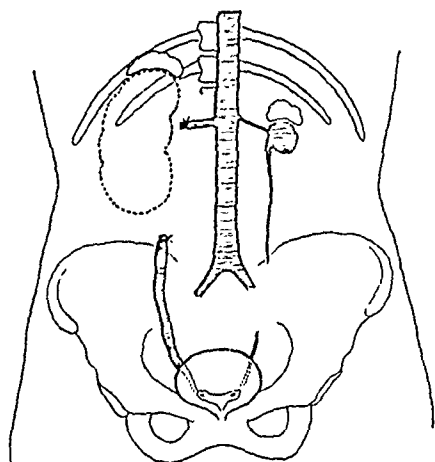


Fig. 12 (case 4).—Drawing in which right nephrectomy was done for multiple cortical abscess of the right kidney in presence of left renal aplasia discovered at postmortem examination. (No pyelogram of this case is available, since it occurred before the establishment of the urologic department.)

was found in the left lumbar region after a full exploration of the intraperitoneal and extraperitoneal cavity. The wound was closed without drainage after the congenital absence of the left kidney was ascertained. The patient suffered with complete suppression of urine and died in uremic coma four days after the second operation. The postmortem examination of this case, performed on December 26, revealed that the right kidney had been removed at operation and that the right renal artery was occluded by a thrombus following ligation of the vessel. In the area of the left kidney a structure was found which represented the remains of an imperfectly developed kidney. This structure gave the impression that the left kidney was present only in a rudimentary stage. Its surface was covered with a fibrous capsule, showing numerous small blood vessels radiating toward the hilus of the organ. A section of the structure revealed the presence of a markedly underdeveloped organ, in which the pyramidal and cortical substance could not be differentiated. The left rudimentary renal artery led to a flat crescent-shaped mass of tissue situated below the left suprarenal, and measuring 3 by 0.8 by 0.6 cm.

(fig. 13). The hilus was occupied by a cystlike structure which represented the pelvis. It was about the size of a bean and was filled with a clear, amber-colored fluid. The interior of this cavity communicated directly with a small, rudimentary ureter, which permitted the passage of a small probe, measuring 2 mm. in diameter. The lumen of this ureter was partially patent, and was found to be rudimentary. It was like a thin cord adhering to the peritoneum, and consisted of a separate upper and lower part without any connecting passage. A photograph of the specimen removed at postmortem examination showed an aplastic renal artery and a ragged mass of aberrant renal substance. A small portion of the



Fig. 13 (case 4).—Photograph of specimen removed post mortem showing the abdominal aorta, an enlarged left suprarenal gland and a mass of aberrant renal tissue representing an aplastic kidney, in which can be seen a rudimentary renal artery, coming from the aorta, and also a rudimentary functionless ureter (see case report).

ureter was constricted, but apparently without the formation of a renal pelvis or calices. On each side of the aorta, however, a thick and enlarged suprarenal was present.

The histologic section of this mass of tissue revealed the presence of embryonic glomeruli and tubules, thereby implying that it was a case of renal aplasia.

This case is a startling lesson and is very instructive in that it brings out the importance of preliminary cystoscopy and complete

urologic and urographic examinations in acute or chronic abdominal conditions, where the diagnosis is in doubt—particularly in cases in which urinary symptoms are present—and in which the routine urinalysis shows microscopic pyuria or hematuria. However, back in the days when this patient was operated on, the urologic department in the hospital had not been established, and not every patient was put through the routine urologic examination as today. Account must also be taken of the fact that the patient came to the hospital with acute abdominal

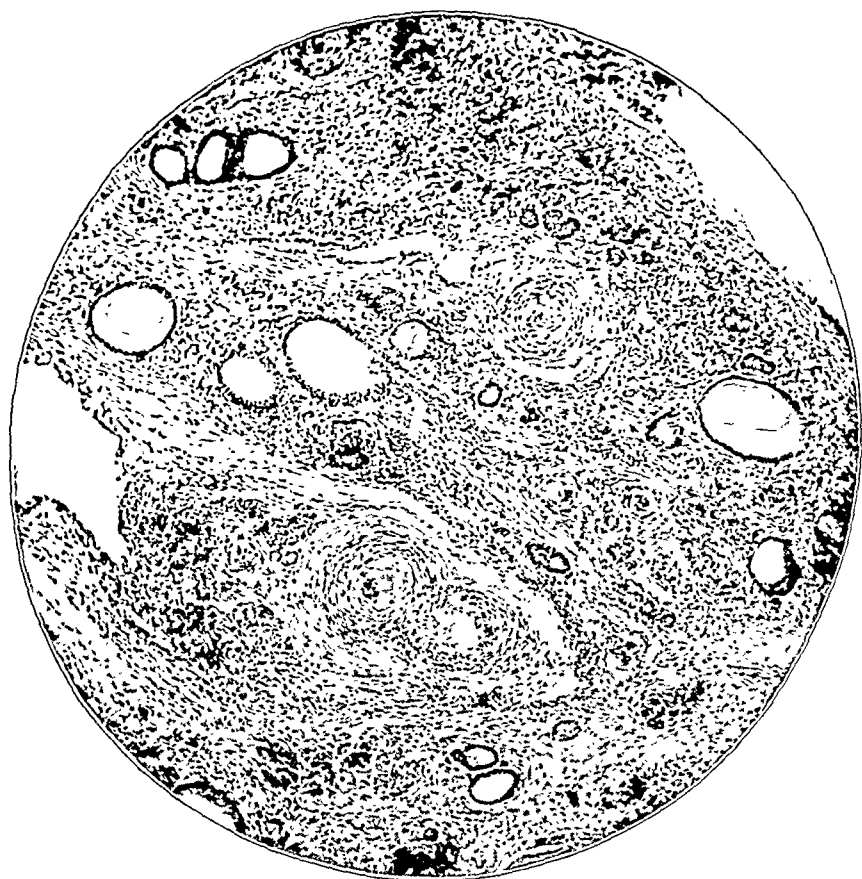


Fig. 14 (case 4).—Photomicrograph of section made from specimen removed post mortem from the left aplastic kidney, revealing the presence of embryonic renal tubules with degeneration and marked hyalinization of the glomeruli, also thickening of the blood vessels and connective tissue. There is a marked tendency to cyst formation of the tubules and the glomeruli.

symptoms, not regarded as kidney disease. The coincidence that cystoscopy is seldom done in the case of a patient menstruating must also be borne in mind. There was, moreover, for immediate consideration the acute condition of the patient, which required surgical intervention without further delay and which unfortunately had a fatal outcome. From this case, as from many others reported in the litera-

ture, the lesson to be learned is that, in operations on the kidney, the surgeon must always bear in mind the possibility of a congenital malformation—lack of function in the opposite kidney, absence or lack of development in one of the kidneys, or the many other varieties of surgical anomalies, which are commonly found in this urographic era of accuracy in diagnosis. This case is obviously a graphic example of renal aplasia with a concomitant pathologic process in its opposite hypertrophic mate, in which type of case only conservative surgical measures and urologic treatment are properly indicated.

#### CONGENITAL ABSENCE OF ONE KIDNEY

Congenital absence of one kidney signifies the complete lack of development of one of the twin organs, and represents a picture in which neither the hypoplastic nor the aplastic condition is present.

The absence of one kidney has been described in the literature from the time of Aristotle.<sup>38</sup> Valsalva,<sup>38</sup> Cruveilhier,<sup>3</sup> Morgagni,<sup>2</sup> Rayer<sup>6</sup> and other writers of a past age have all mentioned this rare anatomic anomaly found at postmortem examination. It has also been found occasionally during an exploratory abdominal operation, but the clinical diagnosis, in advance of operation, was never possible until cystoscopy and urography came into use.

Practically all the cases recorded in the literature up to the urographic era were discovered at postmortem examination. In 1863, Mosler<sup>39</sup> was among the first to make a collection of cases, reporting 14 that he found in the literature. Then Beumer,<sup>40</sup> in 1878, collected 44 such cases. But it was Ballowitz<sup>27</sup> who in 1895, did the important work of collecting and tabulating from the literature the descriptions of 213 cases, many of which were not actually instances of total agenesis of one kidney. Many other cases have meanwhile been reported and the literature has been reviewed on several occasions: by Moore<sup>41</sup> in 1898, by Radasch<sup>42</sup> in 1908, by Anders<sup>43</sup> in 1910, by Dorland<sup>44</sup> in

38. Quoted by Rayer: *Traité des maladies des reins*, Paris, J. B. Baillière, 1841. Morris, quoted by Henry: *Surgical Diseases of the Kidney and Ureter, Including Injuries, Malformations and Mislacements*, London, Cassell & Co., 1901, vol. 1, p. 18.

39. Mosler: *Arch. d. Heilk.* **10**:289, 1863.

40. Beumer: *Ueber Nierendefecte*, *Virchows Arch. f. path. Anat.* **2**:344, 1878.

41. Moore, F. C.: *Unilateral Renal Aplasia*, *J. Anat. & Physiol.* **33**:400, 1898-1899.

42. Radasch, H. E.: *Congenital Unilateral Absence of the Urogenital System and Its Relation to the Development of the Wolffian and Müllerian Ducts*, *Am. J. M. Sc.* **136**:111 (July) 1908.

43. Anders, J. M.: *Congenital Single Kidney with the Report of a Case: The Practical Significance of the Condition with Statistics*, *Am. J. M. Sc.* **39**:313 (March) 1910.

44. Dorland, W. A. N.: *A Consideration of Renal Anomalies*, *Surg., Gynec. & Obst.* **13**:303, 1911.



1911, by Eisendrath<sup>45</sup> in 1923 and by Goldstein<sup>46</sup> in 1925. More recently, Collins<sup>47</sup> of the Mayo Clinic summarized the study of 581 cases of congenital unilateral renal agenesis, among which he has included 9 from the Mayo Clinic, from a series of 6,349 consecutive postmortem examinations, thus representing an incidence of 1 in 705 cases.

It appears, however, that most of the writers who have discussed the abnormality of the absence of a kidney have failed to differentiate this condition from the fused kidney, the aplastic kidney, the hypoplastic kidney and the atrophic kidney, as I have already pointed out. Many authors who have reported cases of unilateral renal agenesis have described the presence of an aberrant aplastic or hypoplastic mass of renal substance, or of connective tissue, or of a rudimentary and incomplete ureter on the opposite side, representing an incomplete development of nephrogenic tissue, which obviously cannot be accepted as the essential and genuine absence of one organ in an anatomic or histologic sense.

TABLE 1.—Cases of Congenital Absence of One Kidney as Collected from the Literature on the Basis of Postmortem Findings

	Number of Cases	Left Kidney Absent	Right Kidney Absent	Side Not Incl- cated	Female		Male	
					Left	Right	Left	Right
Ballowitz.....	213	117	88	8	70	42	31	34
Mankiewicz.....	236	127	97	12	76	47	31	34
Cadore.....	278	136	96	46	78	44	31	32
Cathelin.....	22	10	10	2	1	1	8	7
Campbell.....	10	6	4	..	2	2	4	1
Braasch.....	9	8	1	..	4		5	
Collins, D. C. ....	681	318	238	25	231		281	

Accordingly, from a close scrutiny of the literature with reference to the tabulation and description of all the cases reported, and also from my own observation, I have come to the conclusion that approximately from 35 to 40 per cent are not in reality authentic cases of unilateral renal agenesis, and that this is the reason why some other writers have gone so far as to state that renal aplasia is four time more common than congenital absence of one kidney. Finally, in order to differentiate these three conditions under discussion, I have made a classification based on the clinico-anatomopathologic data which can be seen in the tabulation in the introductory section.

In this section, therefore, I shall deal only with the cases of complete unilateral renal agenesis or congenital absence of one kidney, most commonly described as unilateral solitary kidney. But in the surgical study

45. Eisendrath, D. N.: Congenital Solitary Kidney, *Ann. Surg.* **79**:206, 1924.

46. Goldstein, A. E.: Congenital Absence of One Kidney: Review of Literature and Report of Two Cases, *South. M. J.* **18**:750 (Oct.) 1925.

47. Collins, D. C.: Congenital Unilateral Renal Agenesis, *Proc. Staff Meet., Mayo Clin.* **6**:581 (Sept. 30) 1931.

of congenital absence of one kidney, the cases fall into two groups when regarded from a clinico-anatomopathologic point of view. The first group contains the type of the true solitary single kidney in which there is complete absence of both the kidney and ureter on the one side. The single renal organ may be found in ectopic or cross ectopic position, but in this type of total agenesis there is only one ureteral orifice opening into the bladder and half of the trigone has not been developed. As a rule, this anomaly is accompanied by some form of congenital malformation, particularly of the genital tract, as can be seen in two of the cases that I am here reporting (cases 5 and 6).

The second group consists of the type of the solitary fused kidney, in which there is evidence of union of two nephroblastemas into one

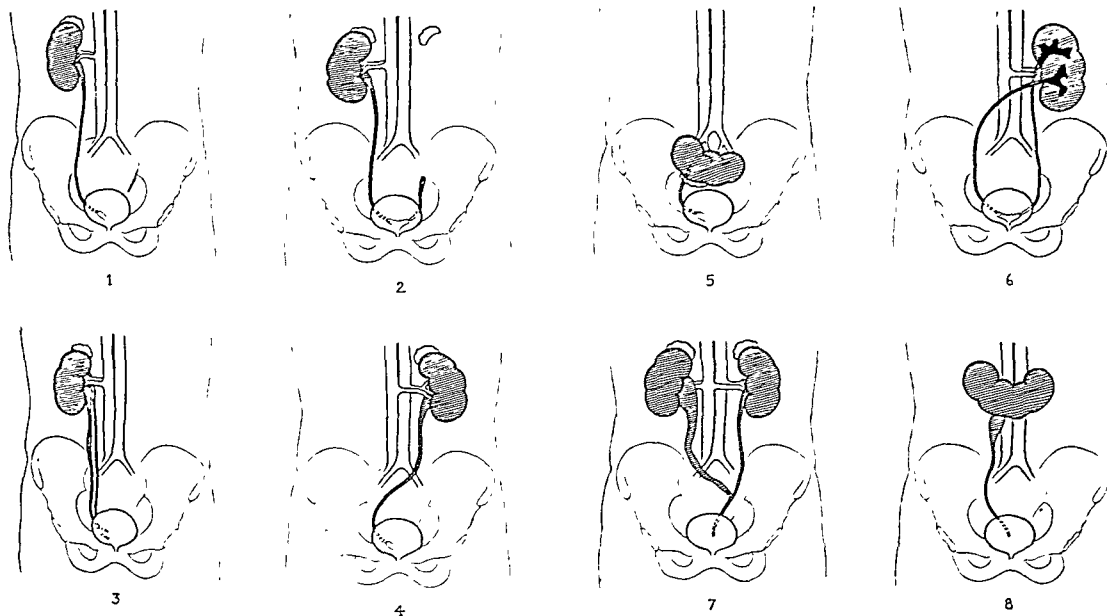


Fig. 15.—Drawing of the different types of congenital absence of one kidney, as collected from the literature: 1, the true congenital solitary single kidney, in which half of the trigone is absent, and there is only one ureteral orifice opening into the bladder (note the absence of the renal artery on the opposite side and also of the corresponding suprarenal capsule); 2, instance erroneously recorded as solitary kidney, when there is anatomic evidence of nephrogenic tissue on the other side; 3, solitary fused single kidney with two ureters opening independently into one side of the bladder; 4, solitary single kidney with ureter in cross ectopia; 5, solitary ectopic single kidney; 6, fused solitary kidney with two pelvises and two ureters in cross ectopia, opening normally into the bladder; 7, the rare instance of a single ureter formed by the fusion of the ureters from two separate kidneys; 8, horseshoe kidney with a single pelvis and ureter and absence of trigone. Note that the essential congenital solitary single kidney is represented in drawings 1, 4 and 5, and that with the exception of 2 and 7, the others are varieties of fused kidney.

organ, characterized by the presence of two pelves and two corresponding ureters, which may open either normally or abnormally into the bladder (fig. 15, nos. 3 and 6). Of this variety of fused kidney, which is so frequently confused in the literature with congenital absence of one kidney, I am reporting an interesting example in case 8 of this series. Elsewhere, I have described<sup>48</sup> the different types of renal fusion, classifying them according as they present a symmetrical or an asymmetrical form of renal union. The symmetrical form is the typical horseshoe kidney, while the asymmetrical embraces such forms of unilateral renal fusion as the L-shaped mass, the sigmoid, the hour-glass, the ring-shaped or the fusion in cross ectopia. All of these are characterized by the presence of two corresponding pelves and two ureters, and hence should not be confused with the true solitary kidney, i. e., the congenital absence of one kidney. Furthermore, in the collection of unusual cases recorded in the literature and portrayed in the drawings of solitary kidney in figure 15, I have inserted the rare condition of a single ureter with two kidneys, an anomaly that has been recorded in the literature only three times, by Hepburn,<sup>49</sup> von Hansemann<sup>50</sup> and Braasch,<sup>51</sup> who made the diagnosis in vivo by pyelography. This condition, no doubt, is misleading in the diagnosis because there is only one ureteral orifice opening into the bladder and because clinically or cystoscopically there appears to be a single solitary kidney, when in reality it is a single ureter with two separate kidneys. Obviously, this rare anomaly can be discovered by the intravenous urographic method or by the routine method of taking ascending and descending pyeloureterograms.

Embryologically, the complete absence of one kidney is best explained hypothetically as a developmental defect of organic origin, in which the nephrogenic membrane or elements of the wolffian duct undergo an arrest in their development of the primitive nucleus, which never has been formed on the one side; hence the corresponding half of the urinary apparatus is absent from the earliest period of intra-uterine embryonic life. It is also of interest to note in this connection the marked frequency with which genital anomalies are met in these cases of unilateral renal agenesis. The corresponding müllerian duct on the agenic side is also absent, and this embryonic defect is directly responsible for the absence of the genital organs, obviously more strikingly observed in the female than in the male, because the genital organs

48. Gutierrez, R.: The Clinical Management of the Horseshoe Kidney, *Am. J. Surg.* **14**:657 (Dec.) 1931; **15**:32 (Jan.); 345 (Feb.) 1932.

49. Hepburn, quoted by Eisendrath.<sup>45</sup>

50. von Hansemann, quoted by Papin: *Chirurgie du rein*, Paris, Doin & Cie, 1928, vol. 1.

51. Braasch, W. F.: The Clinical Diagnosis of Congenital Anomaly in the Kidney and Ureter, *Ann. Surg.* **56**:726 (Nov.) 1912.

of the female are derived from the müllerian duct. It should, therefore, be assumed that the absence of vagina and uterus or any other important anomaly of the genital tract in the female suggests the enormous probability, amounting almost to a rule, that there is also congenital absence of one kidney. The incidence and multiplicity of these varieties of anomalies of the genital tract have been well discussed in the literature, and according to the statistics on record they are met with in approximately 70 per cent of cases where one kidney is absent.

Since the Ballowitz report appeared in 1895, the association of genital and renal anomalies has been further emphasized by Guizzetti and Pariset,<sup>52</sup> Winter,<sup>53</sup> Bolaffio,<sup>54</sup> Engel,<sup>55</sup> Eismayer,<sup>56</sup> Papin,<sup>57</sup> Eisen-drath,<sup>45</sup> and more recently by Collins.<sup>47</sup> The last-named author has recorded the presence of 338 genital anomalies in 581 cases of congenital solitary kidney, 129 being in males and 209 in females.

It is obvious that, with the multiplicity of embryonic malformations of both the genital and the urinary system, one may reasonably expect that the complete absence of the nephroblastema elements will rather frequently involve some other anatomic structures. When the kidney is absent, it is clear that the blood supply on that side is also absent, and the aorta at autopsy shows, in fact, no evidence or vestige of any branch of a possible renal artery on the agenetic side of the body.

It is significant from an embryologic and histologic point of view that the suprarenal gland is developed from two different sources which combine to form the complete organ. It is known that the cortical and the medullary portions of the suprarenal are formed from two different tissues. The cortical portion is derived from the columns of cells which bud off from the wolffian body, and is therefore of mesoblastic origin. The medullary portion of the gland, on the other hand, is developed in connection with the sympathetic nervous system and so is mainly of epiblastic origin. Hence, as the nephrogenic tissues of the wolffian duct are absent and have not developed the definitive kidney, it is assumed that the suprarenal, lacking one of its essential elements, is also absent.

This embryo-anatomohistologic conception of the derivation and formation of the suprarenal gland offers a basis for a new theory, that when a kidney is not formed the suprarenal gland on the corresponding agenetic side is likewise not formed. This theory may serve to estab-

52. Guizzetti and Pariset: Beziehungen zwischen Missbildungen der Nieren und der Geschlechtsorgane, *Virchows Arch. f. path. Anat.* **204**:372, 1911.

53. Winter: *Arch. f. klin. Chir.* **69**:611, 1903.

54. Balaffio: *Ztschr. f. Geburtsh. u. Gynäk.* **68**:261, 1911.

55. Engel, D.: *Beitr. z. path. Anat. u. z. allg. Path.* **67**:549, 1920.

56. Eismayer, G.: Malformations of the Uterus and Kidney, *Ztschr. f. urol. Chir.* **11**:191 (Jan.) 1923.

57. Papin, E.: *Chirurgie du rein*, Paris, Doin et Cie, 1928, vol. 1, p. 137.

predisposing to urinary stasis, owing to lack of drainage plus infection, hydronephrosis or stone formation, most commonly terminating in anuria, fatal uremia and death. The literature, in fact, abounds in reports of cases of anuria and death due to a solitary single kidney, and the report from the Mayo Clinic,<sup>47</sup> is very convincing when the condition of the remaining kidney is described as normal in 281, diseased in 179 and not stated in 121. There were 110 subjects who died from disease of the genito-urinary tract, namely, pyelonephritis, 27 cases; nephrolithiasis, 24; ureterolithiasis, 16; chronic nephritis, 13; hydronephrosis, 12; renal tuberculosis, 4 and infarction and carcinoma of



Fig. 16 (case 5).—Pyelo-ureterogram showing a solitary ectopic single kidney lying in the midline of the bony pelvis in a patient suffering from pyelonephritis and chronic uremia.

the single kidney, each a case. In addition, there are records of many errors in diagnosis and death from operations unwittingly performed on the single kidney.<sup>58</sup> Also Young,<sup>59</sup> Eisendrath,<sup>45</sup> Collins,<sup>47</sup>

58. André: Anurie calculeuse dans un rein unique, *Ann. d. mal. d. org. génito-urin.* **29**:123, 1911. Cathelin: Le rein unique au point de vue chirurgical, *Bull. méd.* **23**:87, 1909. Eliot: Etiologie, pathogénie, traitement de l'anurie, Thèse de Paris, 1910. Albarran, J.: Néphrectomie dans un rein unique, *Assoc. franç. d'urol.*, Paris, 6th session, p. 133. Guinard: Néphrectomie droite pour pyonéphrose calculeuse, mort: rein unique, *Bull. Soc. de chir. de Paris* **36**:1077, 1910.

59. Young, H. H.: *Young's Practice of Urology*, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 11.

Ransohoff,<sup>60</sup> Campbell<sup>22</sup> and other writers have cited from the literature 12 deaths following nephrectomy performed on the solitary single kidney.

The solitary single kidney is anatomically and physiologically enlarged, owing mainly to the compensatory functional hypertrophy. The weight of the single organ is approximately double that of a normal kidney, and in view of its having been overworked through carrying on the total excretory function, the organ undergoes a certain degree of degeneration of its elements, ending in a marked degree of hyperplasia. At the same time that it is pathologically enlarged, chronically inflamed and adherent to the surrounding tissue, it becomes painful and exquisitely sensitive to pressure and palpation, giving rise to abdominal symptoms which in many instances have been taken for chronic appendicitis and other conditions erroneously diagnosed.

The single kidney does not eliminate a sufficient amount of urine, and there is evidence of other metabolic disorders of pluriglandular origin, such as cutaneous neurofibromatosis, adiposity, hypertrichosis, cutaneous pigmentation and neurodermatitis. There is marked hypothyroidism, produced in all probability by lack of sufficient elimination and by autointoxication, causing reflex symptoms, hypogenetic function and a chronic uremic condition, in which the patient's body sometimes gives off a strong odor of urine. Obviously the chemical analysis of the blood reveals enormously high figures in the concentration of urea, creatine, creatinine and other constituents. The elements of the urine are also highly concentrated, and the total output is sometimes not even half of what should be eliminated in twenty-four hours.

When the history of a woman of nervous and irritable type is taken and she mentions that she has never menstruated, and when on physical examination absence of external and internal genital organs is observed, then even in advance of urologic examination a diagnosis of congenital absence of one kidney can potentially be made, as in cases 5 and 6 here reported. In case 7, this could be proved cystoscopically and urographically, and in all three cases the diagnosis was confirmed on operation.

These patients suffering from congenital malformation of a solitary single kidney must be treated in a conservative way, both surgically and urologically. In cases in which there is evidence of pyelitis and pyelonephritis with pus in the urine, marked oliguria and other urinary disorders and uremic symptoms, the patient should receive cystoscopic treatments consisting of lavage of the pelvis of the kidney, even using in acute conditions the method of the indwelling ureteral catheter in order to secure drainage and to correct infection. This was done in

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<sup>60</sup> Ransohoff, J.: *Surgery of the Kidney, the Ureter and the Suprarenal Gland*, in Keen, W. W.: *Surgery*. Philadelphia, W. B. Saunders Company, 1912, vol. 4, p. 200.

case 5 on several occasions, and by this means the patient was saved from fatal uremia.

Operations on the solitary single kidney for removal of stone may be urgently indicated. The most suitable procedure to use, after the kidney or the ureter has been exposed in the usual manner, is either pyelostomy or ureterostomy, which should be regarded as the method of choice. The single kidneys bleed profusely on account of the marked

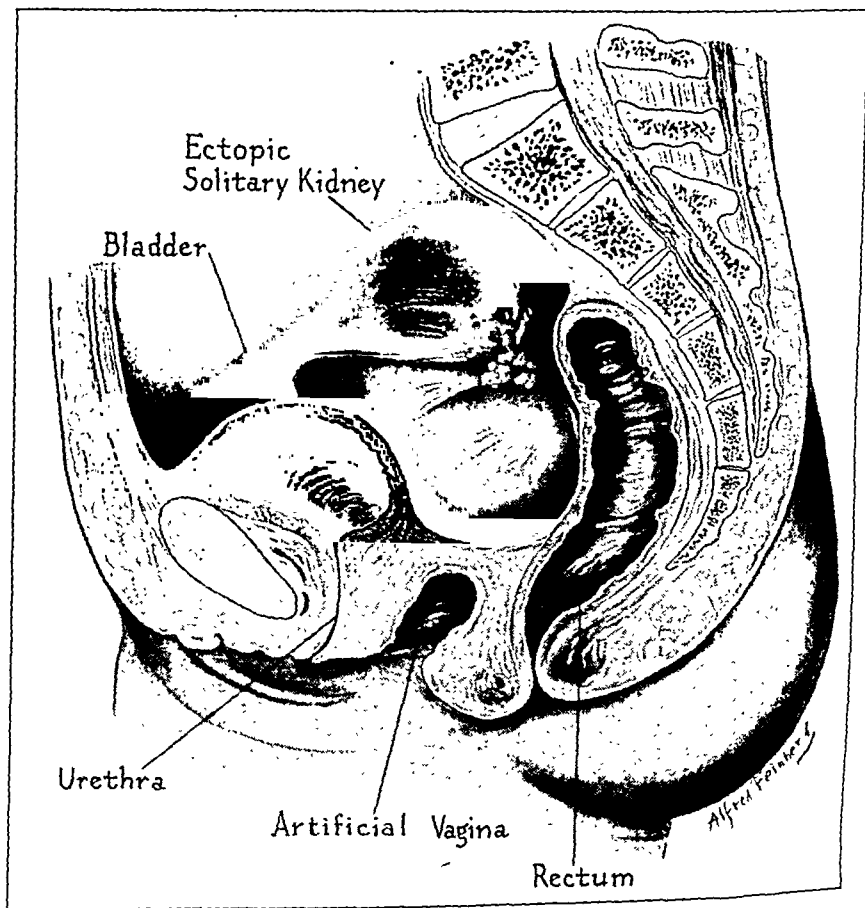


Fig. 17 (case 5).—Drawing of a sagittal view, showing the solitary ectopic single kidney lying between the bladder and the rectum, and also revealing the absence of all genital organs in a patient in whom an artificial vagina had been constructed.

degree of hyperplasia and parenchymatous nephritis present; hence, when nephrotomy or nephrostomy for drainage or for the removal of a stone is done, it should be regarded as a last resort.

Finally, it is essential that, in calculous disease or in anuria of the solitary single kidney, perfect drainage either from below or from above be obtained urologically or surgically, in order to secure the elimination

of urine, thereby assuring the restoration of function and securing preservation of life.

*CASE 5.—Congenital absence of one kidney, the solitary organ being an ectopic single kidney, lying in the midline of the bony pelvis, associated with the congenital absence of vagina and internal genital organs.*

Mrs. E. F., aged 32, was admitted to the ward of the first surgical division of the New York Hospital at midnight of July 11, 1931, in a critical condition. On admission, her chief complaint, she stated, was a pain in the abdomen which she had had for a week and which during the last three days had become very severe, accompanied by nausea, vomiting, dysuria, frequency and burning on urination. The pain was constant and sharp, located in the right lower quadrant and radiating toward the umbilicus and the right lumbar region. She gave a history of having had hematuria several times following an attack of pain; she had also suffered from chronic constipation and had never menstruated.

On physical examination the patient was seen to be an overdeveloped woman for her age, rather obese, chronically ill, with a hypothyroid constitution. The past personal history was of interest. She stated that ten years previously she was operated on for construction of an artificial vagina, and there was a history of her having had two more abdominal operations for adhesions. The vaginal plastic operation was followed by gonorrhea. She has been married twice and has led a very miserable life.

Gynecologic examination showed much congestion and redness of the external genital organs, also scars of the plastic operation; no normal genital organs could be made out. The meatus of the urethra and the clitoris were normal.

Rectal examination revealed no palpable uterus or ovaries, but there was an enlarged tumor mass, rather mobile, which extended up to the umbilicus in the median line and was painful on pressure and free from the rectal wall. With these findings, many tentative diagnoses were made at the time of admission, and the impression was that of an abdominal tumor: (a) ovarian cyst, (b) fibromyoma of the uterus, or (c) retroperitoneal sarcoma.

On July 13, cystoscopy was performed. Examination showed a single right ureter with absence of one half of the trigone and the left ureteral orifice. The right ureter was readily catheterized, but the catheter met with an obstruction about 5 cm. from the bladder. Intravenous administration of indigo carmine was then given. Three and one-half minutes after the injection, it appeared from the right kidney, and no excretion was noticed in the bladder, urethra or vagina. It was therefore assumed that the patient had a right solitary kidney. Roentgenograms were taken before and after injection of sodium iodide into the pelvis of the right kidney. A pyelogram revealed an ectopic solitary right kidney. A week later iopax was administered intravenously and a pyelogram confirmed the findings in the other. The patient was discharged from the hospital as improved two weeks later with the advice that she return to the female urologic clinic, where I have been treating her for the last six months. Owing to the anomalous position of the ectopic solitary kidney, she is still suffering from abdominal pains. She is also complaining of chronic uremic symptoms with nausea and vomiting, and has been readmitted twice to the hospital suffering with chronic uremia and acute pyelitis and pyelonephritis; on several occasions an indwelling catheter has been placed in the pelvis of the kidney in order to secure drainage, to correct infection and to relieve the uremic condition.

Meanwhile, she has been having routine cystoscopic treatments in the clinic with lavage of the pelvis of the kidney, which makes her life more comfortable and



relieves her of the urinary symptoms and abdominal pain, allowing the ectopic solitary kidney to exercise a better function and hence preventing the formation of stone or further infection.

*CASE 6.—Congenital solitary ectopic right kidney associated with congenital malformation of the external and internal genital organs.*

Miss F. S., 23 years of age, was referred from the Nursery and Child Hospital for examination on Nov. 4, 1931, by the courtesy of Dr. Kulmer. She had been complaining of pain across the back and also on the lower right quadrant. On physical examination a large palpable tumor mass on the right flank of the abdomen was easily detected. On March 24, 1930, she was operated on in another hospital for chronic appendicitis, at which time an exploratory operation proved the absence of the internal genital organs and revealed a chronic inflamed appendix and

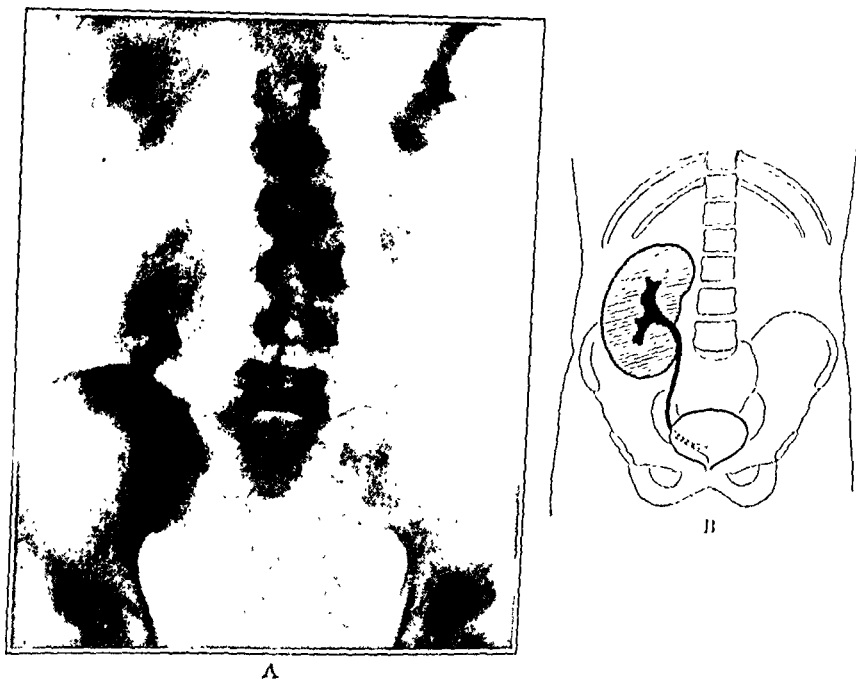


Fig. 18 (case 6).—*A*, pyelogram made following intravenous injection of iopax, revealing the outline of an enormously enlarged solitary ectopic single right kidney. During an exploratory operation for chronic appendicitis the absence of all the genital organs was discovered. *B*, drawing illustrating the position of the ectopic single right kidney, and revealing the coincidence of the congenital absence of one kidney with congenital absence of the vagina.

a retroperitoneal tumor mass, which was believed to be a floating kidney. The patient had no vagina, palpable uterus or ovaries. Although she was well developed for her age, she had never menstruated and had been complaining of slight frequency of urination day and night, with slight dysuria, in addition to the indefinite pain in the lower portion of the abdomen. The physical examination was negative except for the palpable tumor mass on the right side of the abdomen, which was tender on pressure. Analyses of the blood and urine gave negative results. Cystoscopic examination proved the absence of the left side of the trigone, and also the presence of only one ureteral orifice on the right side of the bladder. The single ureter was catheterized, and the urine obtained was clear. Indigo carmine,

given intravenously, appeared in three minutes in the right single kidney. No other indication of blue was seen in the bladder, in the vagina or in the external genital organs. X-ray pictures and pyelograms revealed a single enlarged, hypertrophic and ectopic right kidney, occupying the right lumbo-abdominal-ischial fossa. To ascertain this diagnosis, an intravenous injection of iopax was given a week later, whereupon the pyelogram also confirmed the same discovery—that the left kidney was absent. The right kidney, which was well visualized, showed a marked degree of dystopia and compensatory hypertrophy, thus proving the presence of a solitary congenital ectopic right kidney. There was no shadow indicative of stone anywhere in the urinary tract. A diagnosis was made of congenital absence of one kidney associated with congenital malformation of the external and internal genital organs, and with absence of the vagina. In this case the diagnosis was

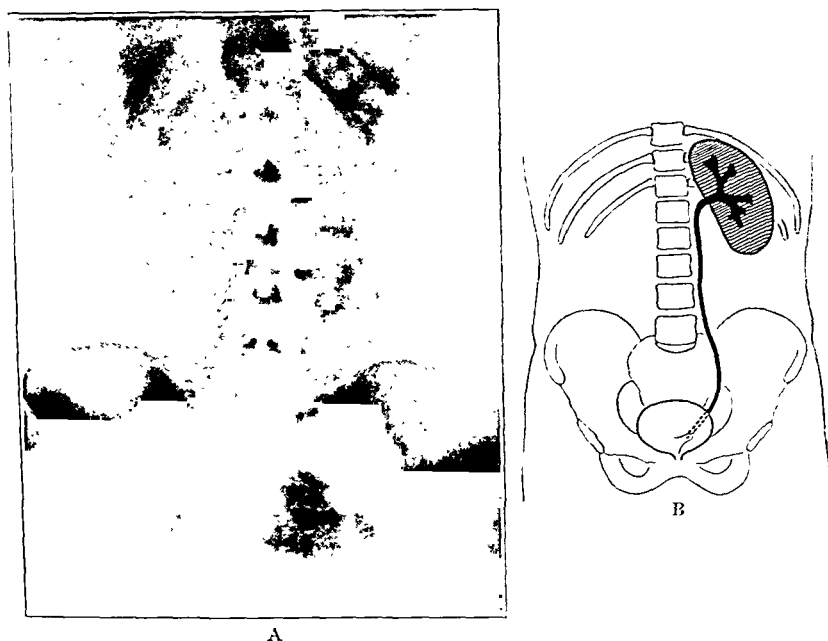


Fig. 19 (case 7).—*A*, pyelogram made after the intravenous administration of iopax, revealing an enlarged left single kidney normally placed, in which diagnosis was made cystoscopically, functionally and urographically by both the ascending and descending methods, and was finally confirmed at operation during an exploratory laparotomy for chronic appendicitis. *B*, drawing to illustrate the congenital malformation with absence of the right kidney and of one half of the trigone.

correctly established clinically by the cystoscopic and functional findings as well as by the intravenous method of pyelography, and it was also confirmed by the abdominal exploratory operation.

*CASE 7.*—*Congenital absence of the right kidney, the left being a solitary hypertrophic organ in normal position; diagnosis made cystoscopically and pyelographically and confirmed at operation.*

Miss E. K., 26 years of age, a private patient of Dr. R. S. Ferguson, by whose courtesy I am reporting this case, was well nourished and well developed. Her chief complaint was an indefinite pain in the abdomen with frequency of urination

during both day and night. She was first seen on March 20, 1930, and cystoscopy was done on April 3. At that time, no right ureteral orifice could be found throughout the bladder, urethra or neck of the bladder. Indigo carmine appeared at the left ureteral orifice three and a half minutes after intravenous injection. No secretion could be observed from the right side of the bladder. A roentgen examination and a pyclogram of the left side revealed the outline of a normally placed left kidney. No renal shadow of the right kidney was visualized. On April 10, cystoscopy was performed again, and when a careful examination of the interior of the bladder failed to reveal any right ureteral orifice, an intravenous injection of iopax was given. The pictures taken showed a normal secretion of the opaque substance in five minutes in the apparently normal left kidney, while on the right side there was no shadow or elimination in several hours. It was, therefore, concluded that there was a congenital absence of the right kidney and a solitary kidney on the left side. No shadow indicative of stone could be seen anywhere in the urinary tract. On June 9, the patient was operated on for a sudden acute attack of appendicitis. At that time a thorough exploration of the right side of the abdomen and the entire pelvis failed to reveal the presence of either a right kidney, a ureter or any rudimentary structures which might be interpreted as belonging to the right half of the urinary tract. The left kidney was palpable and appeared slightly larger than normal. Its position and contour, however, were normal, and the left ureter was also normal. The patient made an uneventful recovery, leaving the hospital in good condition two weeks after the operation. This diagnosis of a congenital absence of the right kidney with a solitary, hypertrophic, single kidney on the left side was made cystoscopically and pyclographically, and was confirmed at operation.

*CASE 8.—Congenital solitary kidney fused in such a manner as to give the impression of being a solitary single organ; ureters in cross ectopic position with the right ureter passing across the midline to reach the solitary double fused kidney; two pelves and two corresponding ureters opening normally into the bladder; diagnosis made roentgenographically and pyclographically in a patient suffering from birth with chronic appendicitis and chronic constipation.*

Miss C. R., aged 24, was admitted into the third surgical division of the New York Hospital on Jan. 7, 1932, and was referred to the urologic department by Dr. W. Cornell. She complained of pain in the right side of the abdomen and stated that for years she had had pain of a recurrent type on the right side. She also gave a history of nausea and vomiting. Three days previously she had a general examination by her family doctor, who advised immediate hospitalization and an operation for the removal of her appendix. Her past history was otherwise irrelevant. She had been constipated all her life and had had to resort to laxatives and enemas. The menstrual and the genito-urinary histories were essentially normal. Apparently she had never had urinary symptoms, although the routine urinalysis during her stay in the hospital showed a cloudy urine, and microscopic examination of the sediments revealed the presence of a few pus cells, for which reason she was advised to have a complete urologic examination before undergoing the operation for the so-called chronic appendicitis. The cystoscopic examination disclosed a normal bladder with two normally placed ureteral orifices. The ureters were catheterized, and the specimen from each kidney was sent to the laboratory for culture estimation of urea and microscopic study. One cubic centimeter of phenolsulphonphthalein, given intravenously, appeared on both sides in two and a half minutes with good concentration. X-ray pictures taken with catheters and instruments in position disclosed the fact that the right catheter, instead of going up into the right lumbar region, passed across the vertebral column to meet with

the kidney of the opposite side. Both catheters were injected with 20 per cent solution of sodium iodide and the pyelograms and pyelo-ureterograms which were taken showed the unusual condition of a fused solitary double kidney with two independent pelves and two ureters opening normally into the urinary bladder. When the diagnosis of this rare congenital malformation of a solitary fused kidney was made, it was believed that, as the right ureter extended across the midline and passed across the great abdominal vessels of the blood, nerve and lymphatic supply, the pressure of these structures interfered with its dynamic contractions and was possibly responsible for the indefinite abdominal symptoms from which the patient had been suffering from birth. It was also noted that there was definite narrowing of the lumen of the right ureter with evidence of pyelitis and pyelonephritis, for which cystoscopic treatments were given, consisting of dilatations of the ureters

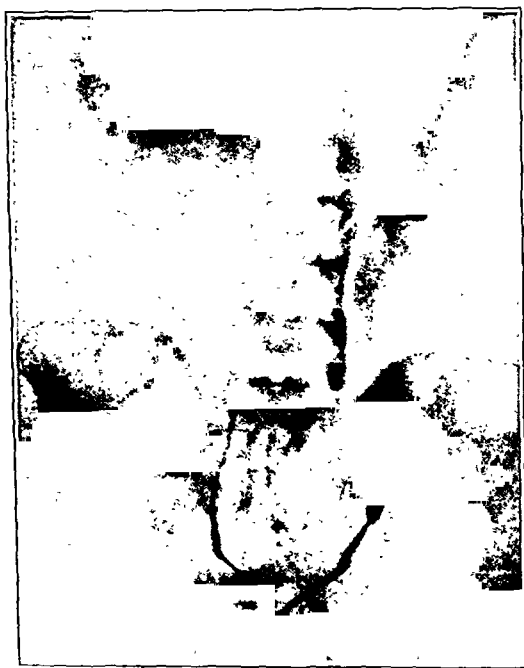


Fig. 20 (case 8).—Pyelo-ureterogram, revealing a solitary left fused kidney with two pelves and two ureters in crossed ectopia, both opening normally into the bladder, with pyelitis and pyelonephritis in a patient suffering from so-called chronic appendicitis.

and lavage of the pelvis of the kidney, in order to relieve infection and secure better drainage. The patient was discharged on January 12, unimproved, but before she left the hospital iopax was administered intravenously and a pyelogram was taken which served to confirm the foregoing findings.

Although this case is not the typical picture of congenital absence of one kidney, it is reported here because of its extreme rarity and because the parenchyma of the kidney in itself had assumed such a form and size as to resemble a solitary single kidney; also, because of its surgical and urographic importance for reaching a correct diagnosis

previous to operation. Finally, this case serves to point out that a cystoscopic examination with a differential renal functional test is not sufficient for obtaining a clearcut diagnosis, until roentgenography and urography combined are employed. They are, therefore, of paramount importance to the surgeon, since without them, he may be led to perform an operation in the dark with fatal results.

#### SUMMARY AND CONCLUSIONS

The study of these three different entities together with the report of two cases of hypoplastic kidney, two of renal aplasia and four of congenital absence of one kidney has served to bring out the confusion that has prevailed in the past and the difficulty in recognizing clinically these three borderline conditions of unique importance in renal surgery.

It has revealed that it is now possible, by means of accurate urologic and urographic examinations, to recognize and differentiate before operation the three conditions of hypoplastic kidney, renal aplasia and congenital absence of one kidney.

The three tables here described not only summarize these conditions but also serve to classify and differentiate them clinically, surgically and anatomopathologically.

In all the eight unusual cases here reported, except case 4, the patients are alive and diagnosis has been made clinically by cystoscopy, by the differential renal functional test and by intravenous and retrograde pyelography; and the diagnosis has also been confirmed at operation in all cases except case 8 in which operation was not indicated.

The etiology underlying these malformations of the kidney must be conceived as based on a congenital defect of embryonic origin, in which an arrest of development has occurred during the cycle of embryonic life. The failure of the wolffian duct of the mesonephros to give off a renal bud is responsible for the presence of total agenesis and for the multiplicity of varieties of kidney malformations that are commonly found during life or at postmortem examination.

The recognition of the hypoplastic kidney is of extreme importance to the urologist and the surgeon, because it is obviously well demonstrated that when nephrectomy is done in its mate for associated pathologic process, the infantile or hypoplastic kidney is incapable of undergoing compensatory functional hypertrophy in order to sustain life.

In the hypoplastic kidney the ureter is always patent, and the excretory function is present. The renal function is diminished in regard to the estimation of urea and elimination of phenolsulphonphthalein, although the excretion of indigo carmine may appear to be within normal limits. The diagnosis must, therefore, be based on pyelographic data.

The condition of renal aplasia is mainly characterized by an arrest of embryonic development in which the kidney has never been formed and the amorphous renal mass has no eliminatory function, while the ureter, although opening into the bladder, is not patent and is accordingly devoid of function.

The diagnosis of renal aplasia can be readily made cystoscopically and pyelographically by combining the use of the retrograde and the intravenous method of pyelography. The histologic sections made of the specimens removed at operation or at postmortem examination reveal the presence of rudimentary renal tissue characterized by an embryonic type of glomeruli and tubules, as can be seen in the two cases here reported (cases 3 and 4).

These two conditions of hypoplasia and aplasia must not, however, be confused with secondary renal atrophy or the destruction of one kidney due mainly to disease or an associated pathologic process of long standing. In the latter condition, the kidney undergoes complete destruction; its parenchyma degenerates and its cortical and medullary substance are lost, as has been commonly observed in the autonephrectomy produced by renal tuberculosis, nephro-ureterolithiasis and other types of lesions. This condition can also be produced experimentally, which is obviously not the case with the entities just described.

The treatment of unilateral hypoplastic kidney and renal aplasia is surgical and consists of the removal of the infantile organ or the amorphous rudimentary mass of tissue, provided the kidney of the opposite side is compensatorily hypertrophied and is performing enough function to sustain life.

The congenital absence of one kidney is differentiated from hypoplastic kidney and renal aplasia by the total absence of nephrogenic tissue on the one side and hence by the complete absence of the corresponding ureter and kidney, and of one half of the trigone, on the same side. It is also important to note that the suprarenal gland on the agenetic side is likewise commonly absent, which is not the case in renal aplasia or hypoplastic kidney.

The solitary kidney may be found in ectopic or cross ectopic position, and is characterized by having a single ureter opening into the bladder. It should be differentiated from that type of renal fusion in which the solitary fused organ has two pelves and two ureters opening independently into the bladder.

The coincidence of renal and genital anomalies is greater than has been suspected, and suggests that when there is a congenital malformation of the genital organs, particularly in the female, the great probability is that there is also lack of development of nephrogenic tissue and hence of one of the twin renal organs, as in cases 5 and 6.

The recognition of solitary single kidney requires careful scrutiny both clinically and at operation, and even at autopsy. Many cases are

recorded in the literature as total unilateral agenesis in which there is, in fact, evidence of the presence of nephrogenic tissue in the agenetic side of the body. The classification and differentiation now presented tend to separate clinico-anatomopathologically these three borderline conditions, which have been the subject of much confusion in the past.

The solitary single kidney is peculiarly subject to disease and in that event carries a fatal prognosis. The association of a pathologic process—parenchymatous nephritis, stone formation, pyelitis and pyelonephritis with a tendency to hydronephrosis, oliguria, infection, anuria and death—has been commonly recorded in the literature. Through errors in diagnosis many operations have unwittingly been performed on the solitary single kidney followed rapidly by anuria and death. In these modern days of exquisite accuracy in the urologic and urographic diagnosis, no operation should ever be performed on either kidney without previous assurance of the presence of its fellow.

The symptomatology of the three conditions under discussion is insidious. The presence of bilateral abdominal pain with an enlarged palpable mass in one side of the abdomen, may signify hypertrophy of one kidney and demands a careful urologic investigation of the upper urinary tract. Nevertheless, sole reliance should not be placed on the intravenous urographic findings, despite the brilliancy of the achievements of this new method, for it cannot be too strongly emphasized that in many cases retrograde bilateral pyelograms are indispensable.

The localization of a pathologic process or disease of the kidney or ureter on the one side does not exclude the necessity of complete investigation of the opposite side also.

Anomalies of the upper urinary tract are commonly met with in this urographic era, and whenever present should be regarded as potentially surgical, in view of their liability to cause stagnation of urine, infection and loss of function, resulting in serious pathologic conditions.

The congenital absence of one kidney does not incapacitate its owner for the normal physiologic functions of life. According to recent statistics, patients with a solitary single kidney live an average of from thirty-five to forty years, and the cause of death may be disease totally unrelated to the genito-urinary tract.

40 East Sixty-First Street.

#### ABSTRACT OF DISCUSSION

DR. C. L. PEACOCK, New Orleans: Dr. Gutierrez's classification is a most excellent one and, so far as I know, the only one in literature differentiating hypoplasia, aplasia and agenesis. One point should be emphasized, and that is the importance in renal surgery, and the necessity, of bilateral pyelograms and kidney functional tests.

DR. THOMAS D. MOORE, Memphis, Tenn.: It is not uncommon for the question to arise as to whether one is dealing with the congenital absence of a kidney.

In a case recently reported the following data seemed to indicate a left renal agenesis: The patient was a young woman who had a right hydronephrosis of 240 cc. capacity; there was no objective evidence of a left ureteral orifice; intravenous injections of indigo carmine and phenolsulphonphthalein appeared from the right orifice only; excretion urography disclosed no evidence of the media in the region of the left kidney; a catheter passed to the right kidney and left in situ for a period of seventy-two hours took care of the entire amount of urine excreted, none being voided about the catheter as would have occurred with a functioning left kidney. In the roentgenogram there was no evidence of a left renal shadow. On physical examination a kidney could not be palpated on the left side. The right hydronephrosis responded in a satisfactory way to a pyelo-ureteroplasty. In another case, however, essentially the same data were obtained, except that the absence of the right kidney was indicated and on the left side a pyonephrosis was superimposed on a renal neoplasm terminating fatally. Necropsy disclosed the error of the assumption that there was a congenital absence of the right kidney; the organ was a mere shell of almost paper thinness and filled with about 100 cc. of thin cloudy fluid. This case illustrates how easily one can be mistaken in the diagnosis of renal agenesis and the necessity of a direct anatomic observation of the renal area, either by surgical exploration or by necropsy, before the positive statement is justified that there is congenital absence of a kidney.

Excretion urography has proved to be of value in the diagnosis of renal aplasia. Recently a small rudimentary kidney was demonstrated by this means; definite compensatory hypertrophy had occurred in the opposite organ.

DR. I. G. DUNCAN, Memphis, Tenn.: I wish to report a case which I believe to be one of congenital absence of a kidney.

The patient was a young white woman, aged 26, who had always menstruated very scantily and irregularly. She came to the gynecologic service of the Baptist Hospital. At operation it was found that the left side of the uterus was undeveloped. There was no tube or ovary on the left side. Following the operation urinary difficulties had developed. I was called in consultation. Cystoscopy was done and it was found that the left side of the bladder was undeveloped. There was no sign of the ureteral ridge or of an orifice. The right side was normal. We injected indigo carmine intravenously and watched carefully. A strong dye came down on the right side but none whatsoever from the left side of the bladder. Later we made intravenous injections of skiodan. No dye showed on the left side, but a large hypertrophied kidney was demonstrated on the right. It is my impression that the left kidney was absent. The pain was on the right side and the trouble seemed to be of a pyelitic nature. Since no operation was performed, we cannot say positively whether there was a total absence, but by all the means used we were unable to demonstrate the presence of kidney tissue on that side.

DR. THOMAS D. MOORE, Memphis, Tenn.: Dr. Gutierrez pointed out the differential diagnosis of aplasia and agenesis in an interesting and clear way. We cannot be 100 per cent sure until necropsy is performed. In one case, that of a young woman, there was no shadow on the roentgenogram; by urographic examination, no medium appeared in the left kidney; on functional tests, no dye appeared on the left side, and no kidney was palpable on physical examination. On those findings it was concluded that no kidney was present on the left side. This patient made an excellent recovery following pyeloplasty, but it was not known positively whether she had a solitary kidney.

In another case there was no evidence of a kidney on the right, although all the methods of examination were carried out that were used in the first case. That patient died, and on necropsy a mere shell of a kidney was found on the



right, where it had been assumed that there was a solitary kidney. The bag was of almost tissue paper texture, and there was no function remaining. This shows how mistaken one can be in these cases.

I wish to emphasize the value of urography in demonstrating these findings. In a recent case a small rudimentary kidney was demonstrated quickly by this method.

DR. H. W. E. WALTHER, New Orleans: I have had one case of infantile kidney. The patient was a girl of 17 who was beginning her university work and was the captain of her basketball team. She was driven to seek medical relief because of intense pain in the right lumbar region. Urography revealed an infantile kidney. Nephrectomy was done and she was completely relieved. She had been studied by several physicians and had been told that if she wore a belt and stopped athletics she would be all right. She did not feel that she wanted to give up her activities, and as we had a high percentage of phenolsulphonphthalein from the opposite side and a zero reading from the painful side it was thought best to operate.

I wish to ask Dr. Gutierrez if, in these infantile kidneys, intense pain is a prominent symptom.

DR. ROBERT GUTIERREZ, New York: Dr. Walther is correct. In hypoplastic kidney the predominating symptom is pain on the side where the lesion is established. This is well explained both pathologically and physiologically. Due to lack of development, the kidney is diminutive or rudimentary in size. The pelvis is small, the emptying time is greatly diminished and retention is produced. Thus, sooner or later, a hydronephrotic crisis gradually develops. As this hypoplastic kidney is incapacitated for sustaining life, it is most important, when nephrectomy is to be done on the opposite side, that the condition be urographically recognized before operation. At no time has such a kidney been larger than when first discovered. It is, therefore, a true congenital lack of development. As infection results from lack of drainage and proper function, the only correct indication is nephrectomy, provided that the lesion is unilateral and that the kidney on the opposite side is normal or functioning sufficiently to sustain life.

I have observed in renal aplasia that the aberrant, functionless mass of renal tissue also produces the characteristic pain in the side. The proper indication is an exploratory lumbotomy in order to remove the aberrant renal tissue. Only by a complete urologic and urographic examination can a definite diagnosis be reached and these two conditions of hypoplastic kidney and renal aplasia be properly differentiated.

The literature has reported many cases of congenital absence of one kidney, in which at postmortem examination a mass of aberrant renal tissue has been discovered on the side opposite to the supposedly solitary organ. This anatomic or histopathologic observation obviously revealed the presence of nephrogenic tissue, which in turn proved the true existence of a hypoplastic or aplastic kidney. A study of these cases has disclosed the frequency of coincidental congenital malformations of the genital tract, particularly in the female.

I wish to place special emphasis on the importance of taking bilateral pyelograms, when a congenital malformation of the upper urinary tract is suspected. Renal tests alone are often misleading in the diagnosis. Recently one of our colleagues reported a case in which nephrectomy was done for infected hydronephrosis. The patient died a few days later in an uremic coma. At postmortem examination a hypoplastic kidney was found, proving that the kidney, although having a certain amount of function, was incapable of undergoing the compensatory hypertrophy necessary to sustain life.

The purpose of my presentation has been primarily to draw attention to these three hazardous conditions of the kidney, so commonly confused in the literature, and to offer a method of proper differentiation, recognition and classification of these three unique conditions. With this object in view, I have drawn up the three tables, which I have just shown.

Do not overlook the possibility of these pathologic and unique conditions of the kidney, for such an oversight may not only mislead in the diagnosis but also result in a fatal prognosis. I wish you the best of luck in properly recognizing these conditions since otherwise you may encounter the sad experience of having removed a solitary single kidney.

were present in the outer cutis and sweat glands in the deeper cutis. Some of the latter were cystic, but there was no evidence of papillary ingrowth.

The third patient was a girl of 12, whose scalp had been burned with hot water, leaving a scaly and papillomatous tumor which increased in size and looked like a condyloma. Histologically, the structure was about the same as in the first case.

Pick believes that all these tumors are the result of congenital disturbance of the sweat gland anlage, and so they are nevi. It is difficult to determine from what part of the ectoderm they take their origin. Two main views are offered. The first, supported by Kreibich, is that the tumor cells take their origin from hair anlage. The second,

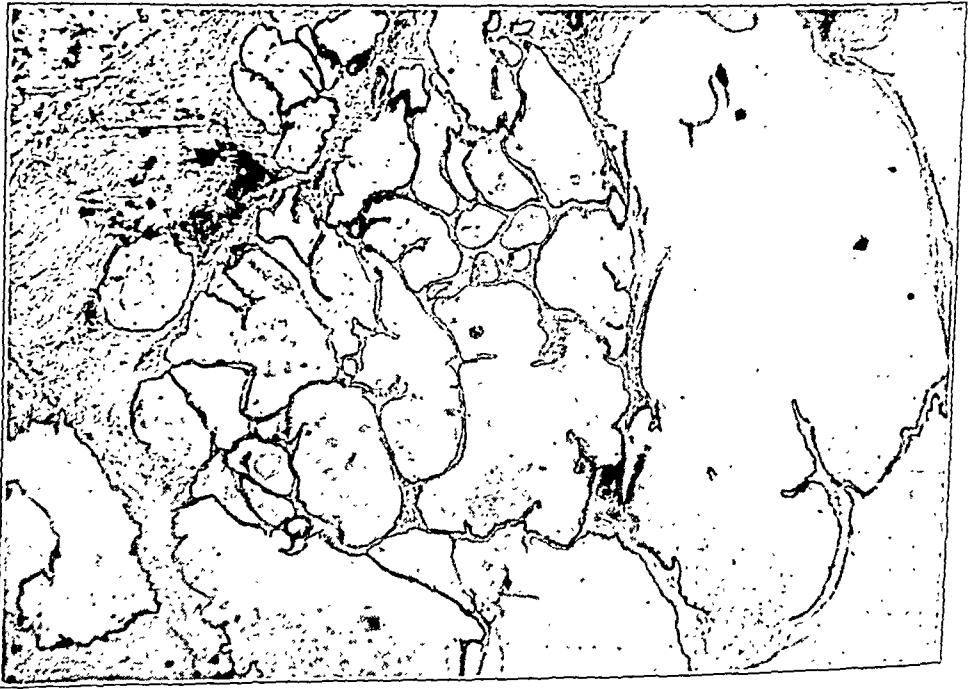


Fig. 2.—Section through part of the specimen, showing the cystlike spaces with some papillomatous ingrowth from the lining walls. The cysts vary in size. Some of them are distinctly tubular in their proliferation.

supported by the majority of authors, is that they take their origin from sweat gland anlage. As a matter of fact, the germinal layer of epithelium has a power of developing sweat glands, hair or sebaceous glands. It is from this germinal epithelium that the tumor cells originate. Consequently, they may have the power to develop any of these structures.

In 1926, Biberstein<sup>3</sup> reported three cases.

3. Biberstein, Hans: Ueber Papilliforme Syringo-Cystadenome, Arch. Dermat. u. Syph. 152:602, 1926.

The first patient was a woman, 45 years old, presenting a growth on the scalp the size of a large coin, with papillary excrescences; it had been present since birth. The growth was partially epithelialized and partially eroded and granulated. Histologic examination of the tumor showed that it was made up of loose stroma of connective tissue cells. The surface covered one or two layers of cylindric cells, and from this surface epithelial cords ran downward. In places these were hollowed out to form tubules. They branched and intertwined, forming a complicated structure. The tubules were lined with two layers of epithelium, and from this arose papilliform projections into the lumen. The spaces in the stroma were closely packed with plasma cells. There were no hairs, sebaceous glands or normal sweat ducts.

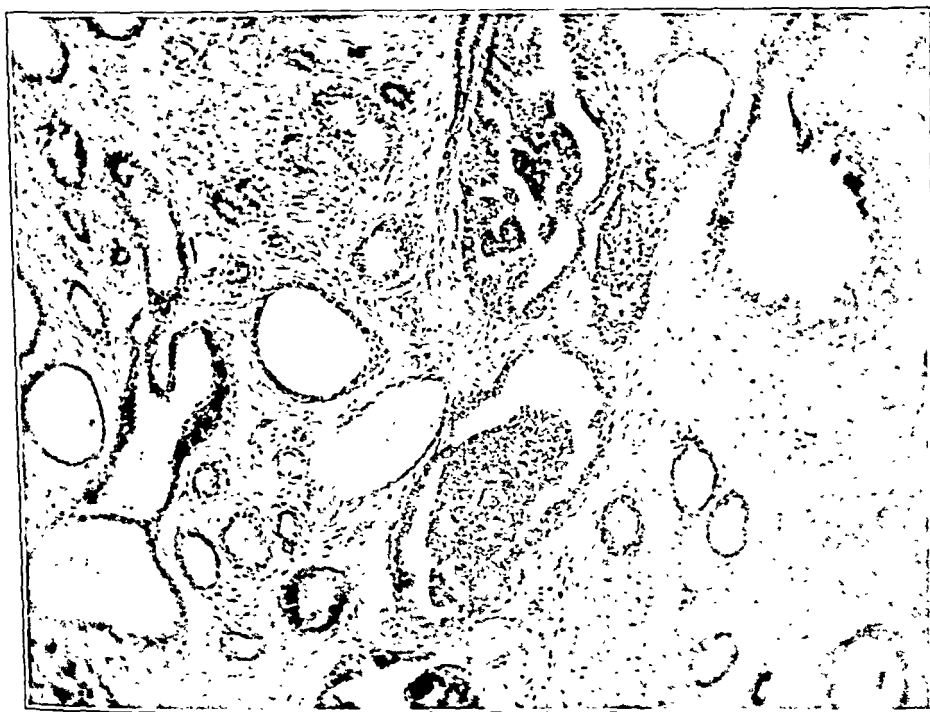


Fig. 3.—Section through another portion of the specimen, showing the papillary proliferation of the tubule and cyst lining, which in some instances nearly fills the lumen. Deeply staining plasmocytes in the surrounding tissues are characteristic. There is no definite evidence of malignancy.

The second patient was a woman of 29, who had a tumor in the scalp which had been present for three years. It was coin-sized, flat and slightly raised, with a morulated surface and papillary projections from the surface. Histologically, it was similar to the tumor in the first case, except that there were normal sweat glands in the corium beneath the tumor, and in two instances these sweat glands showed a definite tendency to proliferation.

The third patient was a girl of 11 years who presented a tumor on the left side of the thorax of three years' duration. The growth was a flat, round nodule the size of a finger-nail; it had a warty surface, and the color resembled that of

*lupus vulgaris*. Histologically, the tumor was made up of tubules and cysts with ingrowing papillomatous proliferation of epithelium. These were surrounded by plasma cell infiltrates. The large cystic areas were connected with deeper lying sweat ducts which were larger than normal, the epithelial lining of which had a tendency to bud into the lumen.

These tumors are clinical and histologic entities, because the epithelium that lines the cysts and tubules proliferates into the lumen in the form of simple or much branched papillae resembling papillary



Fig. 4.—Section cut through the long axis of a tubule which appears as a sweat gland. The lumen is filled with the proliferated lining and a mass of cell detritus. Plasmocyte cells are numerous and characteristic. The tumor is evidently benign.

cystadenoma of the ovary or breast. This papillary ingrowth differentiates the tumors from simple hydrocystomas on one hand and from tubular cystadenomas of the vulva on the other hand. The structure is so characteristic that it cannot be mistaken histologically (figs. 2, 3 and 4).

The typical tumor of which the one shown in the illustrations is an example is chiefly made up of cystic, dilated tubules. About the

tumor cells may be found typical nevus cells in some instances and usually large numbers of well developed plasma cells. Malignant transformation of this adenoma is possible and has been reported by Hedinger. In the lumen of the cystic structure, between the papillomatous excrescences, one finds cell detritus and a sort of slime which reminds one of the material found in simple sweat gland adenomas.

The interesting points in the literature and their relation to clinical diagnosis, especially when the tumor involves the breast, have been summarized by Biberstein:

1. The location of the tumor mass may be either in the very superficial part of the skin or may be deep in the cutis.

2. The content of the cysts is colloidal in some cases; in others it is a fine, granular, homogeneous, eosinophilic mass.

3. Branches have been described, which when present form tubules. These may be in part solid strands or cords of cells and in part tubules.

4. Papillary excrescences of the inner wall into the lumen of the tubules or the cysts are often found, as in intracanalicular papillomas. These were present in most of the cases reported, and at times there were excretory ducts which opened on the surface.

5. Solid strands of cells may be made up of cells of basal cell type, of flat epithelial cells or, as in some cases in the literature, of cells which resemble sebaceous gland cells.

6. There is more or less dense accumulation of plasma cells.

7. Lymphocytic infiltration may be present, but is usually only perivascular.

8. The membrana propria is usually evident in places around cysts, tubules and strands.

9. The general relation of the tumor to the epidermis is often confusing. The strands of the tubules may be connected with epidermis or may even open into it. The cysts may open directly into the epidermis in some cases or through ducts in others, or broad, solid bands of cells may connect the cysts with the epidermis. The tubules may be connected with the epidermis in a similar variety of fashions.

10. The relation of the tumor tissue to sweat glands and to hairs is as follows:  
(a) In one case in the literature the excretory duct apparently opened into the hair follicle. Hair and sebaceous glands may be entirely lacking in the tumor, hair anlage with cysts may be present, or there may be well formed hairs. A sebaceous transformation of some simple cells of the tumor occurred in Krebich's case.

- (b) The sweat glands in Biberstein's three cases were connected with the tumor mass. Unassailable evidence of the connection of the tumor cells with normal sweat glands has been made the basis of calling them sweat gland adenomas by Bartels, Brocq and others. Adenoma-like proliferation of the dilated sweat glands may occur beneath the tumor tissue. Other authors have described transformations from dilated sweat glands to cysts of the type seen in these tumors.

Biberstein believes that these growths are undoubtedly sweat gland tumors, but whether they are adenomas or epitheliomas is a subject of argument. The presence of plasma cells is an evidence of a marked tendency to proliferation, as well as their occurrence at certain ages; whether the tumors are derived from already developed sweat glands or from their anlage cannot be determined.

# INFLUENCE OF HYPERTONIC SALT SOLUTIONS ON THE MOTILITY OF NORMAL AND OF OBSTRUCTED INTESTINE

AN EXPERIMENTAL STUDY

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AND

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NEW ORLEANS

Since the original observations by Hughson and Scarff<sup>1</sup> in 1924 that the intravenous administration of hypertonic sodium chloride solutions increased intestinal movement, these solutions have been employed extensively by clinicians in the treatment of adynamic ileus. Beneficial results obtained by the use of hypertonic sodium chloride solutions have been reported by a number of investigators.<sup>2</sup> In a previous

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From the Department of Surgery, Tulane University School of Medicine.

1. Hughson, W., and Scarff, J. E.: Influence of Intravenous Sodium Chloride on Intestinal Absorption and Peristalsis, *Bull. Johns Hopkins Hosp.* **35**:197, 1924.
2. (a) Ross, J. W.: Hypertonic Saline in Adynamic Ileus, *Canad. M. A. J.* **16**:24, 1921. (b) Coleman, E. P.: Further Observations on Use of Hypertonic Saline Solution in Acute Intestinal Obstruction, *Anesth. & Analg.* **6**:210, 1927. (c) Gosset, A.; Binet, L., and Petit-Dutailis, D.: Toxemia in Intestinal Obstruction: Experimental and Clinical Study, *J. de chir.* **35**:321, 1930. (d) Duncombe, M.: Postoperative Intestinal Occlusion Treated by Ileocolostomy and Intravenous Injections of Hypertonic Salt Solution, *Bull. et mém. Soc. nat. de Chir.* **54**:1482, 1926. (e) Courty, L.: Postoperative Intestinal Occlusion Treated with Intravenous Injections of Hypertonic Salt Solutions, *ibid.* **55**:602, 1929; Acute Intestinal Occlusion Treated by Cecal Anus and Injection of Hypertonic Salt Solution, *ibid.* **54**:1450, 1928; Four Cases of Intestinal Occlusion Treated by Deviation and Intravenous Injections of Hypertonic Salt Solution with "Solu-Camphor," *ibid.* **55**:1335, 1929. (f) Lion, R.: Une observation d'intoxication par occlusion intestinale haute, guérie par injections de chlorure de sodium à haute dose, suivies d'opération, *Bull. et mém. Soc. de chir. de Paris* **21**:141, 1928. (g) Kuss, G.: A propos des injections de sérum salé hypertonique par voie rectale dans l'occlusion intestinale, *Bull. et mém. Soc. nat. de chir.* **54**:1460, 1928. (h) Szuve, in discussion on Duncombe: Postoperative Intestinal Occlusion Treated by Ileocolostomy and Intravenous Injections of Hypertonic Salt Solution, *ibid.* **54**:1482, 1928. (i) Battista, A.: Use of Hypertonic Saline Solution in Intoxication Caused by Acute Obstruction, *Riforma med.* **49**:905, 1929. (j) Dreyer, H. B., and Tsung, Thelma: Effect on Intestinal Movements of Certain Salts Administered Intravenously, *J. Pharmacol. & Exper. Therap.* **36**:629, 1929. (k) Tytgat: Employment of Hypertonic Sodium Chloride Solutions in Intestinal Occlusion, *Ann. et bull. Soc. roy. de méd de Gand* **8**:146, 1929. (l) Clement, F.: Un cas d'iléus post-opératoire traité

investigation,<sup>3</sup> we demonstrated that hypertonic sodium chloride solutions definitely increased intestinal activity. Orr<sup>4</sup> has emphasized the importance of the administration of hypertonic salt solutions (20 cc. of a 10 per cent and 500 cc. of a 5 per cent sodium chloride solution) in the treatment of postoperative gas pains. Reid,<sup>5</sup> working with a Thirty-Vella fistula of the jejunum, showed that the intravenous administration of hypertonic sodium chloride solution not only increased the activity of an intestinal segment but also increased the propulsive type of motility.

In order to determine the effect of various hypertonic salt solutions on the motility of the intestine, the present investigation was undertaken. One hundred and twenty-eight observations concerning the effect of the intravenous injection of salt solutions on the movement of the intestine were made in sixty-five dogs. Of this group, only one hundred and seventeen are used in the present study because in eight a physiologic Ringer's solution was employed, and in three the results obtained could not be used because of a leak in the intestinal balloon. In the three latter cases, there undoubtedly occurred an increase in peristalsis and propulsive activity as evidenced by copious evacuation of the intestinal contents through the enterostomy tube, but because the effect could not be measured the results are not included. Ten observations were made on normal animals, thirteen on animals with twenty-four hour intestinal obstruction, forty-nine on animals with forty-eight hour obstruction and forty-five on animals with seventy-two hour obstruction. In each instance, kymographic tracings were made of the intestinal movements, and the results herein presented are based on an analysis of these kymographic tracings and are not dependent on mere unaided ocular

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avec succes par injections intravéineuses de solution hypertonique de chlorure de sodium, Bull. et mém. Soc. d. chirurgiens de Paris **22**:347, 1930. (m) Bojovitch, V.: Traitement des occlusions intestinales post-opératoires, Presse méd. **38**:1662, 1930. (n) Denis, R.: Indications, mode d'action et posologie des injections de chlorure de sodium hypertonique dans l'occlusion intestinale, *ibid.* **38**:203, 1930; A propos des récentes discussions sur le rôle du chlorure de sodium hypertonique dans l'occlusion intestinale, *ibid.* **38**:906, 1930. (o) Dogliotti, A. M., and Mairano, M.: Notre expérience de trois années dans la thérapeutique salie dans l'occlusion intestinale, *ibid.* **38**:880, 1930. (p) Prati, M.: Intestinal Obstruction: Good Results with Large Doses of Sodium Chloride, Riv. di pat. sper. **5**:168, 1930. (q) Barthelemy: Accidents d'occlusion post-opératoire; injections de sérum salé hypertonique, Bull. et mém. Soc. nat. de chir. **56**:637, 1930. (r) Bouisset, L., and Fabre, P.: Peristalsis in Obstruction; Action of Sodium Chloride, Compt. rend. Soc. de biol. **104**:847, 1930.

3. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: The Value of Drugs in the Relief of Ileus, Arch. Surg. **21**:924 (Dec.) 1930.

4. Orr, T. G.: The Action of Sodium Chloride upon the Small Intestine, Ann. Surg. **94**:732, 1931.

5. Reid, P. E.: Effect of Hypertonic Sodium Chloride Intravenously on Intestinal Peristalsis, Proc. Soc. Exper. Biol. & Med. **29**:220 (Nov.) 1931.



observations. Concomitant respiratory, and in the majority of instances, concomitant blood pressure, tracings were made. In thirty-eight blood pressure tracings were not obtained, because the observations were made on "survival" animals so that exposure and sacrifice of one of the larger arteries was not feasible. In the majority of instances (seventy-nine), observations were made on anesthetized (barbital) animals, the abdomens of which were open and submerged in warm physiologic solution of sodium chloride, as described by Sanders<sup>6</sup> and Alvarez,<sup>7</sup> and as previously used by us.<sup>8</sup> This method will subsequently be referred to as the "open abdomen" technic. In thirty-eight instances, observations were made on unanesthetized "survival" animals according to the "closed abdomen" technic, which is published in detail elsewhere.<sup>9</sup>

It is briefly as follows:

At laparotomy, the terminal ileum is divided and each end inverted and closed. Approximately 5 cm. proximal to the lower end of the upper segment, a fenestrated enterostomy tube is introduced through a stab wound, the enterostomy tube extending proximally into the lumen of the bowel for a distance of about 20 cm. Approximately 5 cm. proximal to this enterostomy opening, a rubber tube carrying a balloon is introduced proximally into the lumen of the bowel for a distance of from 5 to 10 cm. Both of these tubes are brought out through the omentum and abdominal wall, following which the latter is closed. The enterostomy tube is left open. After twenty-four hours with the enterostomy tube still open, the tube carrying the balloon is attached to a Maury tambour and a kymographic tracing taken of the normal intestinal movement, before, during and after the intravenous injection of saline solution. The enterostomy tube is then tied off, producing an intestinal obstruction. After varying periods of time, usually at twenty-four, forty-eight and seventy-two hour intervals, observations concerning the effect of the intravenous injection of hypertonic salt solutions on the intestinal activity are made. The following solutions were used for intravenous injection: sodium chloride solution, 20 per cent; "hypertonic" Ringer's solution; "hypertonic" Hartmann's combined solution; sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent; and sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent.

#### HYPERTONIC SODIUM CHLORIDE SOLUTION

Twenty-four observations were made concerning the effect of 20 per cent sodium chloride on obstructed intestine. In seventeen, the obstruction had existed forty-eight hours, whereas in seven, it had

6. Sanders, H.: *Ezn. Methode tot onderzoek der peristaltische Bewegingen van het darmkanaal, enz. Voorloop. mededeel, abstr., Centralbl. f. d. med., Wissenschaft., 1871, p. 479; cited by Alvarez.*<sup>7</sup>

7. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, New York, Paul B. Hoeber, Inc., 1929.

8. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: *Comparative Value of Splanchnic and Spinal Analgesia in the Treatment of Experimental Ileus*, *Arch. Surg.* **20**:802 (May) 1930.

9. Gage, I. M.; Ochsner, Alton, and Cutting, R. A.: *Effect of Insulin and Dextrose on the Normal and the Obstructed Intestine*, *Arch. Surg.* **26**:658 (April) 1933.

existed seventy-two hours. Three observations (previously referred to) made in one animal are unreliable, because the tracing showed that a leaky intestinal balloon was present, even though the intestine was active as evidenced by copious evacuation of feces through the enterostomy tube. These three observations are omitted because of the inability to measure accurately the effects produced by hypertonic saline solution. In three other instances, there was evidence of a leaky balloon, but the results are included even though the values obtained are probably lower than the true values. The amounts of the hypertonic sodium chloride solution which were administered varied from 2.7 to 10.2 cc., the average being 8.4 cc. per kilogram of body weight. The average amounts administered to animals with forty-eight hour and with seventy-two hour obstructions were 8.7 and 6.2 cc. per kilogram of body weight, respectively. There was an average increase in blood pressure

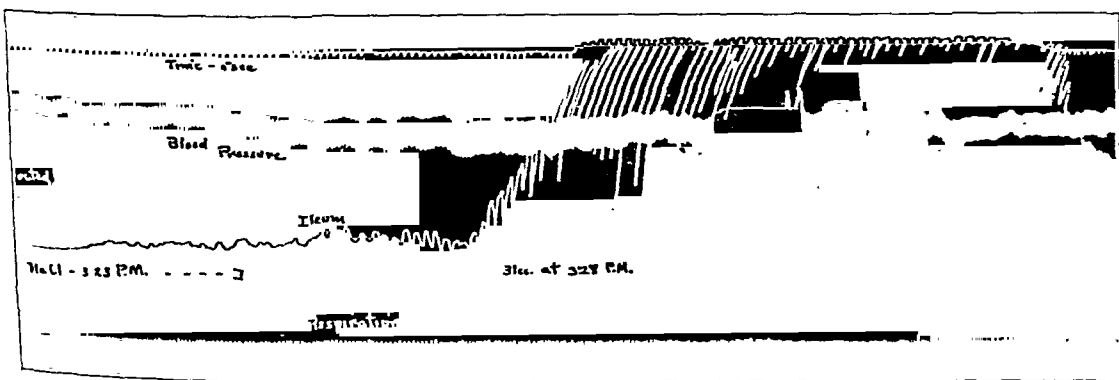


Fig. 1.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous injection of 20 per cent sodium chloride. As shown at the left of the tracing, there was little or no movement of the intestine. Shortly after the beginning of the infusion, there was some activity followed by a marked increase in tone and also an increase in amplitude, the lever almost passing off the drum (open abdomen technic).

of 22 mm. of mercury in 23.5 per cent of the animals with forty-eight hour obstruction. In 64.8 per cent, there was no change in blood pressure; in 5.8 per cent, there was a temporary fall in pressure, and in 5.8 per cent, there was a sustained decrease of 20 mm. of mercury. In all of the animals with seventy-two hour obstruction that received the hypertonic sodium chloride solution, there occurred no change in blood pressure. Of all the animals (both with forty-eight hour and seventy-two hour obstructions) that received 20 per cent sodium chloride solution the blood pressure was increased in 20 per cent (an average increase of 22 mm. of mercury), unchanged in 70 per cent, temporarily decreased in 5 per cent and definitely decreased in 5 per cent. Of the twenty-one observations made following the intravenous administration of 20 per

cent sodium chloride solution, the intestinal activity was increased in nineteen (90.4 per cent), unchanged in one (4.7 per cent) and decreased in one (4.7 per cent). The average increases in intestinal tone and amplitude of intestinal movement in the nineteen in which there was an increased activity were 28.6 and 5.05 mm., respectively. In two instances, there were increases in amplitude of intestinal movement but no associated increases in tone, and in two other instances, there were increases in tone which were not associated with increases in amplitude. The increases in intestinal tone varied from 7 to 80+ mm. The increases in amplitude varied from 0.5 to 40 mm. The average duration of the increased intestinal activity was 11.1 minutes. Of the nineteen observations in which there occurred an increase in intestinal activity, sixteen were made in animals with forty-eight hour obstruction and three in

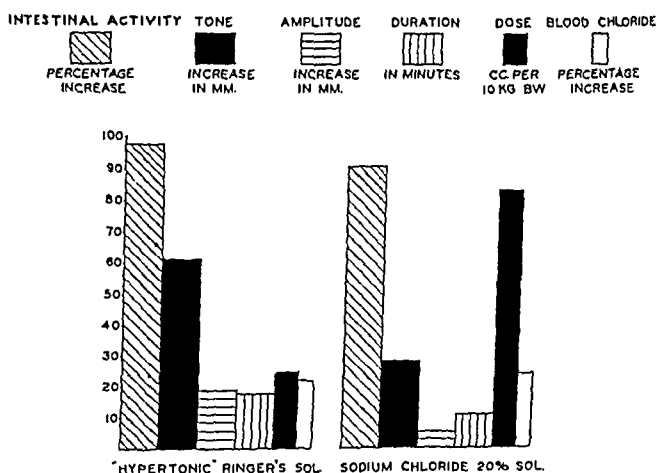


Fig. 2.—Graphic representation of changes in the intestine produced by the intravenous administration of a hypertonic Ringer's solution and of sodium chloride, 20 per cent solution. There was a slight percentage increase in intestinal activity following the administration of the solution. More significant, however, is the character of the change in that the intravenous injection of a hypertonic Ringer's solution produced a much greater increase in tone (solid black), increase in amplitude, and a longer duration of the activity than did sodium chloride, in spite of the fact that the dose of the hypertonic Ringer's solution was less than that of the sodium chloride solution. In the other graphs the various columns denote the same thing.

animals with seventy-two hour obstruction. The average increases in intestinal tone and amplitude in the animals with forty-eight hour obstruction were 20.56 and 2.25 mm., respectively. The average increases in tone and amplitude in those with seventy-two hour obstruction were 71.6 and 20 mm., respectively (fig. 1). The average durations of the increased intestinal activities in animals with forty-eight and the seventy-two hour obstructions were five and twenty-one minutes, respectively. In the one instance (4.7 per cent) in which there

occurred a decreased activity, the tone was decreased 11 mm., but there was no change in the amplitude of intestinal movement (fig. 2, table 1).

### "HYPERTONIC" RINGER'S SOLUTION

Sixty-one observations were made concerning the effect of intravenous administration of a hypertonic Ringer's solution on normal and obstructed intestine. The expression hypertonic Ringer's solution is obviously incorrect as Ringer's solution is a physiologic solution. The hypertonic solution used, however, was obtained by multiplying quantities of salts contained in Ringer's solution by 20. The solution so obtained contained: sodium chloride, 18 per cent; calcium chloride, 0.52 per cent, and potassium chloride, 0.6 per cent. In forty-three instances, the open abdomen technic was used and in seventeen instances, the closed abdomen technic. As the results obtained with

TABLE 1.—Sodium Chloride 20 Per Cent; Open Abdomen Experiments

	Total Observa- tions	Normal Intestine	24 Hour Obstruc- tion	48 Hour Obstruc- tion	72 Hour Obstruc- tion
Number of observations.....	21	....	....	17	4
Average dose per Kg. of body weight, cc.....	8.4	....	....	8.7	6.2
Average blood chloride before, mg. per 100 cc.....	653.5	....	....	657.3	638
Average blood chloride after, mg. per 100 cc.....	804	....	....	802.7	809
Increase in blood chloride, per cent.....	23.1	....	....	22.1	26.8
Increased intestinal activity, per cent.....	90.4	....	....	94.1	75
No change in intestinal activity, per cent.....	4.7	....	....	5.8	0
Decreased intestinal activity, per cent.....	4.7	....	....	0	25
Average increase in tone, mm.....	28.6	....	....	20.5	71.6
Average increase in amplitude, mm.....	5.05	....	....	2.25	20
Average duration increased activity, minutes.....	11.1	....	....	5	21

the closed abdomen experiments differed from those obtained with the open abdomen experiments, the two will be considered separately (fig. 3). Of the forty-three observations made following the intravenous administration of the hypertonic Ringer's solution in which the open abdomen technic was used, fourteen observations were made on animals with forty-eight hour obstructions and twenty-nine on animals with seventy-two hour obstructions. The amounts of the hypertonic Ringer's solution administered varied from 0.6 to 6 cc., the average being 2.5 per kilogram of body weight. The average amount of the hypertonic Ringer's solution administered to the animals with forty-eight hour obstructions was 2.6 cc., whereas those with seventy-two hour obstructions received an average amount of 2.48 cc. per kilogram of body weight. Intravenous injection of the hypertonic Ringer's solution into animals with forty-eight hour obstruction produced an increase in blood pressure in 20.8 per cent. no change in 50 per cent and temporary but slight falls in blood pressure varying from 8 to 30 mm. of mercury (the average 18.8 mm. of mercury) in 28.2 per cent. In 80

per cent of the observations made on animals with seventy-two hour obstruction, there were increases in blood pressure varying from 10 to 30 mm. of mercury, the average being 17.5 mm. of mercury. In 10 per cent, there was no change, and in 10 per cent, there were slight but temporary decreases in blood pressure. In 38.4 per cent of all animals that received the hypertonic Ringer's solution, there were increases in blood pressure, the average being 18 mm. of mercury. In 38.4 per cent, there was no change, and in 23.5 per cent, there were temporary but slight falls in blood pressure. The blood chloride values before the administration of the hypertonic Ringer's solution varied from 554 to 759 mg., the average being 629.8 mg. per hundred cubic centimeters. The blood chloride values after the administration of the solution varied from 721 to 825 mg., the average being 771.2 mg. per hundred cubic centimeters, an average percentage increase in blood chlorides of 22.5. The average blood chloride values before and after the intravenous

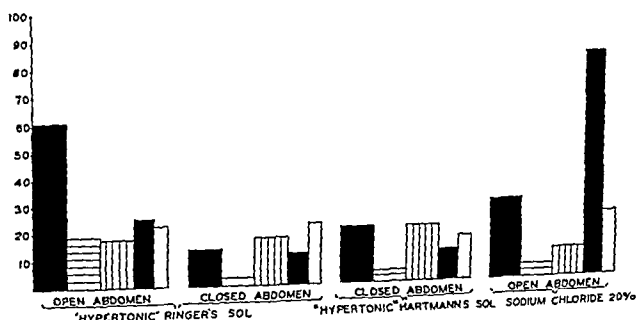


Fig. 3.—Graphic representation of the effect on the intestine of the intravenous administration of a hypertonic Ringer's solution, a hypertonic Hartmann's solution, and of sodium chloride, 20 per cent. A comparison of the results obtained by the open abdomen and closed abdomen technics is made with the hypertonic Ringer's solution. The hypertonic Hartmann's solution (closed abdomen technic) caused a slightly greater increase in intestinal activity than did the hypertonic Ringer's solution (closed abdomen technic).

administration of the hypertonic Ringer's solution in the animals with forty-eight hour obstructions were 659.5 and 785.42 mg. per hundred cubic centimeters, respectively. The average percentage increase in blood chlorides in this group was 19.2. The average blood chloride values before and after the administration of the hypertonic Ringer's solution in the animals with seventy-two hour obstruction were 611.2 and 761.3 mg. per hundred cubic centimeters, respectively, an average percentage increase of 24.5. Of the entire group of forty-three, forty-one (95.3 per cent) showed an increase in intestinal activity, whereas only two (4.7 per cent) showed no change. In one of these, the Ringer's solution was given at the height of the intestinal activity from a previous injection. If this one exception is eliminated, stimulation of the intestinal activity occurred thirty-seven times out of thirty-eight

observations (97.7 per cent). The average increases in intestinal tone and amplitude of movement were 63.8 and 16.07 mm., respectively. The increases in tone varied from 5 to 125 mm., and the increases in amplitude ranged from 2 to 150 mm. The average duration of the increased intestinal activity was eighteen minutes (fig. 2). The increases in tone were probably actually greater than indicated by these figures, because in four instances (all in the group with seventy-two hour obstruction) the true responses are not expressed because of a leaky intestinal balloon. Also, in three instances, the tracing needle passed off the kymographic drum and the true value could not be measured. The true average duration of increased activity was undoubtedly longer than eighteen minutes, because in seven of the forty-three instances, the intestine was still active at the time the observations were terminated.

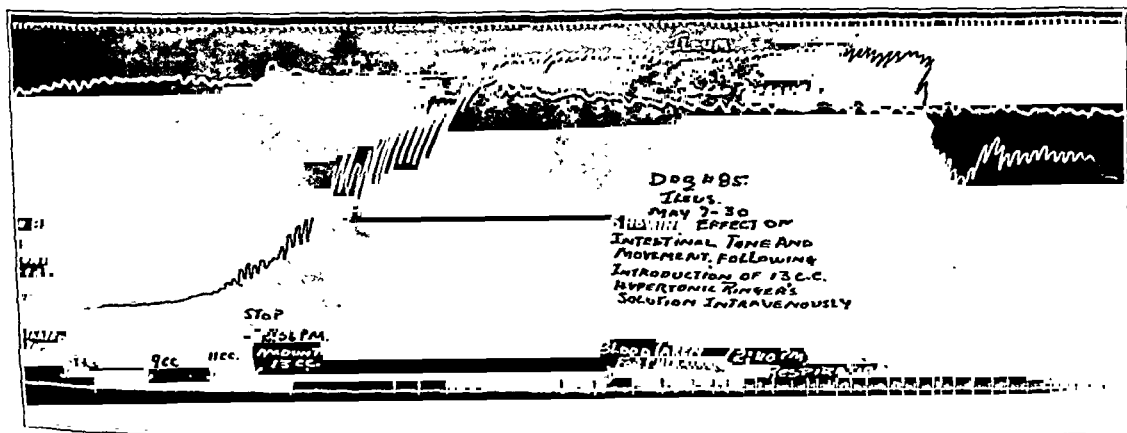


Fig. 4.—Kymographic tracing showing the effect on forty-eight hour obstructed intestine of the intravenous injection of a hypertonic Ringer's solution. At the extreme left of the tracing, the intestine was inactive. After 11 cc. of the solution had been given, there was a rapid rise in intestinal tone associated with an increase in intestinal movement, following which the intestine became more or less spastic. This increased activity was continued throughout the experiment although there was a moderate fall in tone after approximately eight minutes (open abdomen technic).

The average increases in intestinal tone and amplitude which occurred in animals with forty-eight hour obstructions were 62.1 and 11.3 mm., respectively (fig. 4). The average duration of the increased activity was 12.4 minutes. The average increases in tone and amplitude of the intestine of the animals with seventy-two hour obstructions were 64.2 and 18.3 mm., respectively (figs. 5 and 6). The average duration of the increased activity was 20.36 minutes (table 2).

Eighteen observations concerning the effect of the intravenous administration of the hypertonic Ringer's solution on normal and

obstructed intestine of unanesthetized animals with the closed abdomen technic were made. The amount of Ringer's solution administered intravenously varied from 0.7 to 1.7 cc., the average being 1.17 cc. per kilogram of body weight. The blood chloride values before the administration of the hypertonic Ringer's solution varied from 510 to 640 mg., with an average of 588 mg. per hundred cubic centimeters. The blood

Fig. 5.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of a hypertonic Ringer's solution. There was some activity in the intestine before the administration of the solution, as evidenced by periodic movement of the intestine. Following the administration of the solution, there was a marked rise in intestinal tone, which in the beginning was associated with an increased intestinal movement. This was, however, followed by a sustained tone. During this period there was copious evacuation of feces through the enterostomy tube (open abdomen technic).

Fig. 6.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of a hypertonic Ringer's solution. As is seen at the extreme left of the tracing, there was practically no movement of the intestine. Following the intravenous administration of the solution, there was a marked increase in intestinal tone, so much so that the lever almost passed off the drum. This was associated with a definite periodic increase in intestinal movement, which was later followed by a sustained rise in tone (open abdomen technic).

chloride values following the administration of solution varied from 605 to 1,010 mg. (average, 725.3 mg.) per hundred cubic centimeters of

blood. There was an average percentage increase in blood chlorides of 23.4. Of the eighteen observations, three were made on normal intestine, six on intestine which had been obstructed for twenty-four hours, six on intestine which had been obstructed for forty-eight hours and three on intestine which had been obstructed for seventy-two hours. Of the entire group, there was an increase in intestinal activity in seventeen (95 per cent), whereas in one (5 per cent) no change occurred. In those instances in which increased activity occurred, there were average increases in tone and amplitude of 13.1 and 2.9 mm., respectively. The average duration of the increased intestinal activity was 17.6 minutes (fig. 7). In three observations made on normal intestine following intravenous injection of the hypertonic Ringer's solution, there was an

TABLE 2.—*Hypertonic Ringer's Solution; Open Abdomen Experiments*

	Total Observa- tions	Normal Intestine	24 Hour Obstruc- tion	48 Hour Obstruc- tion	72 Hour Obstruc- tion
Number of observations.....	43	....	....	14	29
Average dose per Kg. of body weight, cc.....	2.59	....	....	2.6	2.48
Average blood chloride before, mg. per 100 cc.....	629.8	....	....	639.5	611.2
Average blood chloride after, mg. per 100 cc.....	771.2	....	....	785.4	761.3
Increase in blood chlorides, per cent.....	22.5	....	....	19.2	24.5
Increased intestinal activity, per cent.....	97.7	....	....	92.8	100
No change in intestinal activity, per cent.....	2.3	....	....	7.17	0
Decreased intestinal activity.....	0	....	....	0	0
Average increase in tone, mm.....	63.8	....	....	62.15	64.6
Average increase in amplitude, mm.....	16.07	....	....	11.3	18.3
Average duration of increased activity, mm.....	18	....	....	12.4	20.33

increase in activity in two (66.6 per cent) and no change in one (33.3 per cent). In the latter instance, however, the Ringer's solution was given at the height of intestinal activity, which had been produced by a previous injection of the solution. The average increases in tone and amplitude in this group were 11.5 and 5 mm., respectively. The average duration of the activity was thirty-two minutes. In all (100 per cent) of the six observations made on animals with twenty-four hour obstructions there were increases in intestinal activity, the increases in tone and amplitude being 5.8 and 2.3 mm., respectively (fig. 8). The average duration of the increased activity was 14.3 minutes. In all (100 per cent) of the six animals with forty-eight hour obstructions, there were increases in the intestinal activity following the intravenous administration of the hypertonic Ringer's solution. The increases in tone and amplitude were 23.3 and 3.3 mm., respectively (fig. 9). The average duration of the increased activity was more than fourteen minutes. In the three observations made on the seventy-two hour obstructed intestine, there was an increased activity in all with average increases in tone



and amplitude of 30 and 2 mm., respectively (fig. 10). The average duration of the increased activity was 22.3 minutes (table 3).

Thirty-four observations were made concerning the coagulation of the blood of animals with intestinal obstruction. Twenty-six of these were made before and after the administration of the hypertonic Ringer's solution, whereas in eight, the observations preceded and fol-

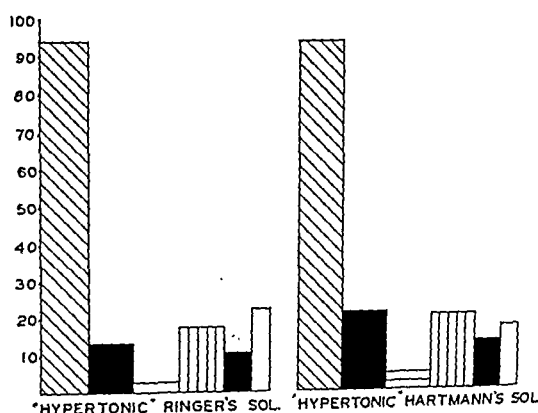


Fig. 7.—Graphic representation showing the effect on intestinal activity of the intravenous administration of a hypertonic Ringer's solution and of a hypertonic Hartmann's solution. The percentage increases in intestinal activity are approximately the same; there are, however, slightly greater increases in tone and in amplitude of movement following the hypertonic Hartmann's solution than that obtained with the hypertonic Ringer's solution.

TABLE 3.—*Hypertonic Ringer's Solution; Closed Abdomen Experiments*

	Total Observations	Normal Intestine	24 Hour Obstruction	48 Hour Obstruction	72 Hour Obstruction
Number of observations.....	18	3	6	6	3
Average dose per Kg. of body weight, cc.....	1.17	1.00	1.02	1.08	1.16
Average blood chloride before, mg. per 100 cc.....	588.93	607.3	589.1	557	590.5
Average blood chloride after, mg. per 100 cc.....	725.3	666.6	728.3	792.5	670
Increase in blood chloride, per cent.....	23.4	9.4	26.8	42.2	12.7
Increased intestinal activity, per cent.....	94.4	66	100	100	100
No change in intestinal activity, per cent.....	5.5	33*	0	0	0
Decreased intestinal activity.....	0	0	0	0	0
Average increase in tone, mm.....	13.1	4.5	5.8	23.3	30
Average increase in amplitude, mm.....	2.9	5	2.3	3.3	2
Average duration of increased activity, minutes..	17.6	32	14.3	14+	22.3

\* Ringer's solution given at height of activity following previous injection.

lowed the administration of morphine. In the latter group, it was found that the average coagulation time before the administration of morphine was two minutes and forty-eight seconds, whereas the average coagulation time following the administration of morphine was two minutes and twenty-five seconds, an average decrease in coagulation time of 13.6 per cent. In all instances in which the coagulation time was determined before and after the intravenous administration of the hypertonic Ringer's solution, there was a decreased coagulation time (increased

coagulability of the blood) following the administration of the solution. The percentage decreases in coagulation time varied from 12.7 to 57, the average coagulation time before and after intravenous injection being two minutes and fifty-four seconds and one minute and fifty-six seconds, respectively, an average percentage decrease of 33.

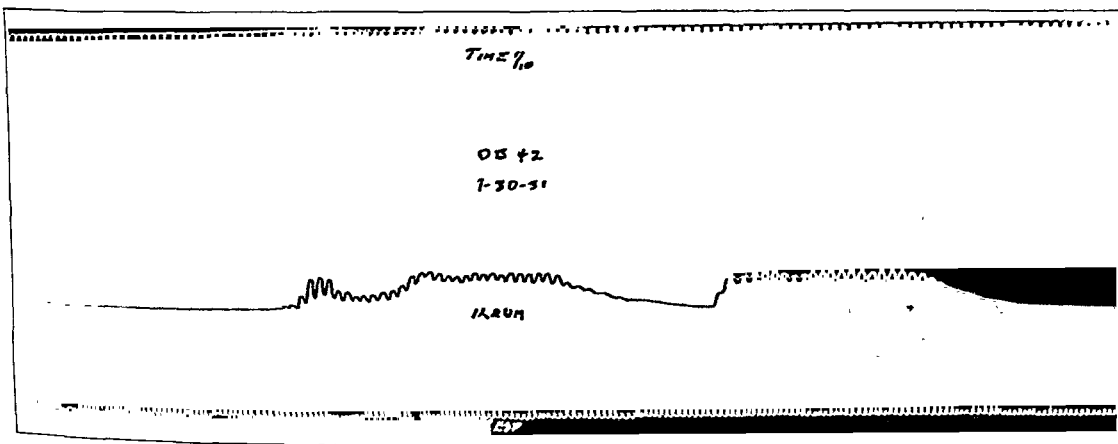


Fig. 8.—Kymographic tracing showing the effect on twenty-four hour obstructed intestine of the intravenous administration of a hypertonic Ringer's solution. As seen at the extreme left of the tracing, there was no activity in the intestine, but following the administration of the solution, there was an increase in intestinal tone and also amplitude of movement. This increase in intestinal movement showed evidence of periodicity (closed abdomen technic).

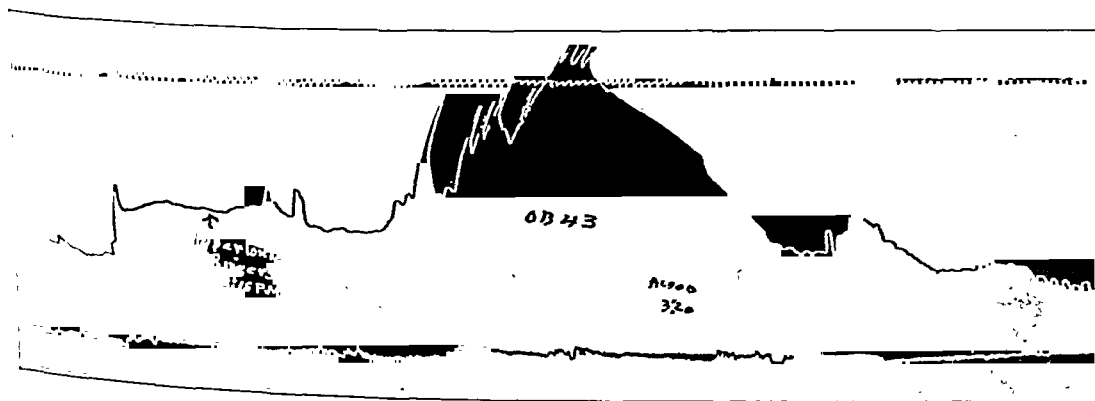


Fig. 9.—Kymographic tracing showing the effect on forty-eight hour obstructed intestine of the intravenous administration of a hypertonic Ringer's solution. Following the infusion, there was a marked increase in intestinal tone associated with an irregular increase in intestinal movement. This increased activity persisted a relatively short time (closed abdomen technic).

In eight instances in which an intravenous injection of a normal Ringer's solution was made into normal animals, there was an increase

in intestinal activity in four (50 per cent) and no change in four (50 per cent). The average increases in tone and amplitude were 35.5 and 2.2 mm., respectively (fig. 11). The average duration of the increased activity was 21.6 minutes.

Fig. 10.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of a hypertonic Ringer's solution. There was a marked increase in intestinal tone which was associated with an increase in intestinal movement. The duration of the increased activity was short (closed abdomen technic).

Fig. 11.—Kymographic tracing illustrating the effect on normal intestine of the intravenous injection of a physiologic Ringer's solution. As seen in about the midportion of the tracing, there occurred following the intravenous administration of 40 cc. of the solution a rapid rise in intestinal tone which was associated with an increase in intestinal movement. During this period of increased activity, the kymographic drum was stopped, the entire period of increased activity being one hour and ten minutes (closed abdomen technic).

#### "HYPERTONIC" HARTMANN'S COMBINED SOLUTION

Twenty observations concerning the effect of the intravenous injection of hypertonic combined solution of Hartmann were made on

animals, the closed abdomen technic being employed. Hartmann's solution<sup>10</sup> is a modified Ringer's solution containing the electrolytes of the blood and also sodium lactate, which is readily oxidized. The solution as now employed by Hartmann is as follows:

Sodium lactate .....	2.80	Gm. per liter
Sodium chloride .....	5.85	Gm. per liter
Potassium chloride .....	0.373	Gm. per liter
Calcium chloride .....	0.274	Gm. per liter

As this solution is being dispensed in a concentrated form in ampules, which facilitates its use, it was thought advisable to test its efficacy in stimulating the intestine. The solution as dispensed is diluted twenty-five times in order to make a physiologic solution. In our experiments, we added to the contents of a 20 cc. ampule, 5 cc. of sterile distilled water, giving a solution with the following constituents:

Sodium chloride .....	11.7	per cent
Sodium lactate .....	5.6	per cent
Potassium chloride .....	0.74	per cent
Calcium chloride .....	0.54	per cent

The amount of the hypertonic Hartmann's solution which was administered varied from 0.18 to 3.2 cc., the average being 1.16 cc. per kilogram of body weight. Blood chloride values before the administration of the solution varied from 476 to 725 mg. with an average of 547.63 mg. per hundred cubic centimeters of blood. The blood chloride values after the administration of the solution varied from 500 to 780 mg., the average being 670.79 mg. per hundred cubic centimeters. There was an average percentage increase in blood chlorides of 16.3. The average amount of the hypertonic Hartmann's solution administered to animals with normal intestine was 1.1 cc. per kilogram of body weight. The average blood chloride values before and after the administration of the solution were 564.28 and 632 mg. per hundred cubic centimeters, respectively, an average percentage increase of 12.2. The average amount of the hypertonic Hartmann's solution administered to animals with twenty-four hour obstructions was 1.4 cc. per kilogram of body weight. The average blood chloride values before and after the administration of this solution were 539.83 and 645 mg. per hundred cubic centimeters of blood, respectively, an average percentage increase of 19.8. The average amount of Hartmann's solution administered to animals with forty-eight hour obstructions was 0.9 cc. per kilogram of body weight. The average blood chloride values before and after the administration of the solution were 712.5 and 739 mg. per hundred cubic centimeters, respectively, an average percentage increase of 3.9.

10. The Hartmann's solution was supplied us by the Eli Lilly Company.

The amount of Hartmann's solution administered to animals with seventy-two hour obstructions was 0.98 cc. per kilogram of body weight. The average blood chloride values before and after the administration of the solution were 672.75 and 745.77, respectively, an average percentage increase of 10.8. Of the twenty observations, in nineteen (95 per cent) there were increases in intestinal activity following the intravenous administration of the hypertonic Hartmann's solution. In only one instance (5 per cent) was there no change in intestinal movement. The average increases in tone and amplitude in the nineteen instances were 20 and 3.6 mm., respectively; the average duration of the increased intestinal activity was 20.2 minutes (figs. 3 and 7). Seven of the twenty observations were made on normal intestine. In 87.5 per cent of these

Fig. 12.—Kymographic tracing showing the effect on normal intestine of the intravenous administration of a hypertonic Hartmann's solution. As illustrated at the extreme left of the tracing, there was little movement of the intestine. Following the infusion of the solution, there was a moderate rise in intestinal tone associated, however, with a very definite increase in intestinal movement (closed abdomen technic).

there was an increase in intestinal activity, whereas in 12.5 per cent there was no change. The average increases in tone and amplitude in this group were 25.6 and 3 mm., respectively, the average duration of the activity being 20.4+ minutes (fig. 12). Seven observations were made on animals with twenty-four hour obstruction, in all (100 per cent) of which there was an increase in intestinal activity. The increases in tone and amplitude were 16.2 and 1.7 mm., respectively (fig. 13). The average duration of the activity was 17.2+ minutes. Both of the observations made concerning the effect of the hypertonic Hartmann's solution on forty-eight hour intestinal obstruction showed an increase

in intestinal activity, the increases in tone and amplitude being 28 and 8.5 mm., respectively (fig. 14). The average duration of the increased activity was 16.5 minutes. In four observations made on seventy-two hour obstructed intestine, there was an increase in intestinal activity



Fig. 13.—Kymographic tracing showing the effect on twenty-four hour obstructed intestine of the intravenous administration of a hypertonic Hartmann's solution which had been given twenty-five minutes previously. As illustrated, there were periodic increases in intestinal activity, consisting of increases in tone and amplitude of intestinal movement (closed abdomen technic).

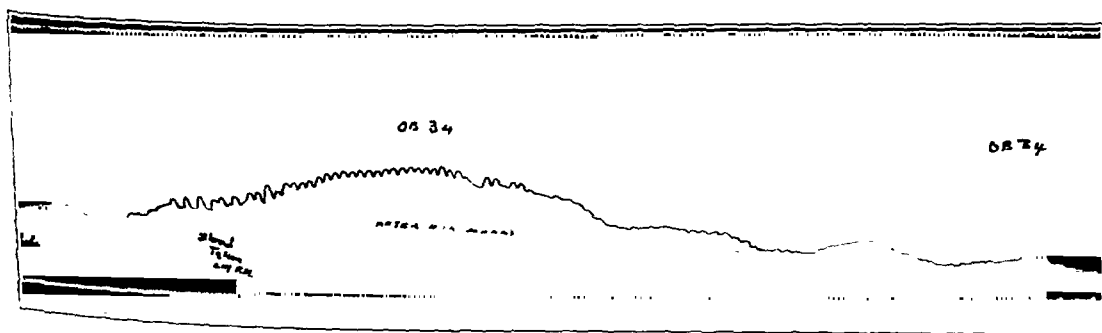


Fig. 14.—Kymographic tracing illustrating the effect on forty-eight hour obstructed intestine of the intravenous administration of a hypertonic Hartmann's solution. There was a slight rise in intestinal tone but a definite increase in amplitude of intestinal movement (closed abdomen technic).

in all. There were increases in tone and amplitude of 13.5 and 5 mm., respectively (fig. 15). The average duration of this increased activity was 28.2 minutes (table 4).

SODIUM CHLORIDE, 20 PER CENT; CALCIUM CHLORIDE, 5 PER CENT

Four observations concerning the effect of the intravenous injection of sodium chloride, 20 per cent, and calcium chloride, 5 per cent, were made on animals with forty-eight hour intestinal obstruction. The amounts injected varied from 2.2 to 4.4 cc., the average being 2.7 cc. per kilogram of body weight. The average blood chloride values before and after the administration of the hypertonic salt solution were 616.2 and 816 mg., respectively, an average percentage increase of 32.5. There were increases in intestinal activity in all instances (100 per cent). The average increases in intestinal tone and amplitude were 25.7 and 12.5 mm., respectively (fig. 16). The duration of the increased activity was 17.2 minutes. In one of the four instances (25 per cent), there was an increase in blood pressure amounting to 16 mm. of mercury.

TABLE 4.—*Hartmann's Solution; Closed Abdomen Experiments*

	Total Observa- tions	Normal Intestine	24 Hour Obstruc- tion	48 Hour Obstruc- tion	72 Hour Obstruc- tion
Number of observations.....	20	7	7	2	4
Average dose per Kg. of body weight, cc.....	1.16	1.1	1.4	0.9	0.98
Average blood chloride before, mg. per 100 cc.....	547.6	564.2	539.8	712.5	672.7
Average blood chloride after, mg. per 100 cc.....	670.7	632	645	739	745
Increase in blood chloride, per cent.....	16.3	12.2	19.8	3.9	10.8
Increased intestinal activity, per cent.....	95	87.5	100	100	100
No change in intestinal activity, per cent.....	5	12.5	0	0	0
Decreased intestinal activity.....	0	0	0	0	0
Average increase in tone, mm.....	20	25.6	16.2	28	13.5
Average increase in amplitude, mm.....	3.6	3	1.7	8.5	5
Average duration of increased activity, minutes..	20.2	20.4++	17.2+	16.5	28.2

In two (50 per cent), there was no change in blood pressure and in one (25 per cent), the carotid cannula became clotted, so that the determinations could not be made (table 5, fig. 14).

SODIUM CHLORIDE, 20 PER CENT; CALCIUM CHLORIDE, 0.5 PER CENT

Five observations were made concerning the effect of the intravenous injection of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent, on obstructed intestine. Three of these were made on animals with forty-eight hour obstructions and two on those with seventy-two hour obstructions. The amount injected varied from 1.58 to 3.7 cc., the average being 2.2 cc. per kilogram of body weight. The blood chloride values before and after the administration of the hypertonic salt solution were 641.5 and 788.5 mg., respectively, an average percentage increase of 22.6. In each of the five instances, there was an increase in intestinal activity with increases in tone and amplitude of 73.8 and 16.6 mm., respectively. The average duration of this increased activity was 19.2 minutes (fig. 16). In the animals with

forty-eight hour obstruction, the average dose per kilogram of body weight was 1.5 cc. Blood chloride values in this group before and after the intravenous administration of the hypertonic salt solution were 641.5 and 788.5 mg., respectively, an average percentage increase of

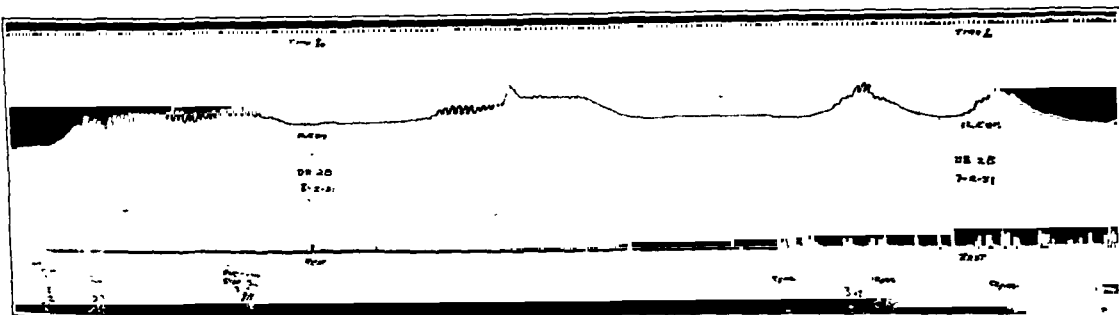


Fig. 15.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of a hypertonic Hartmann's solution. There were periodic increases of intestinal tone and amplitude of intestinal movement. Associated with each increase in tone and amplitude, the animal apparently experienced pain as evidenced by crying (closed abdomen technic).

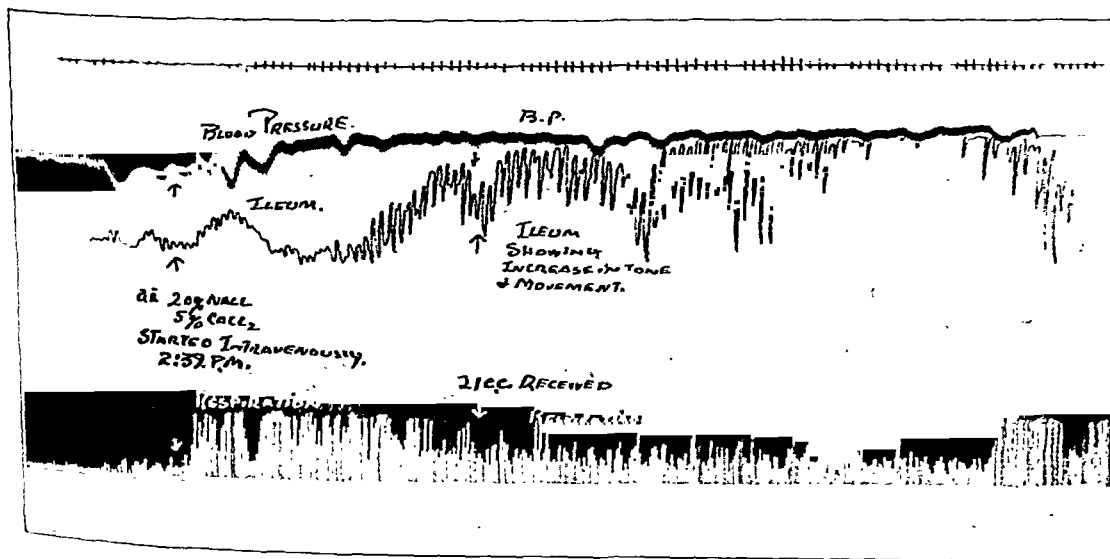


Fig. 16.—Kymographic tracing showing the effect on forty-eight hour obstructed intestine of the intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 5 per cent. There was an increase in intestinal tone but more marked was the increase in the amplitude of intestinal movement. Approximately four minutes after the completion of the infusion, the intestine became more or less spastic (open abdomen technic).

22.6. In all instances (100 per cent) there were increases in intestinal activity, the increases in tone and amplitude being 74.6 and 14 mm..



respectively (fig. 18). The average duration of the increased activity was nineteen minutes. In the two observations made on animals with seventy-two hour obstruction, the average dose per kilogram of body weight was 3.3 cc. The average increases in intestinal tone and amplitude were 72.5 and 20 mm., respectively (fig. 19). The average duration of the increased activity was 19.5 minutes. The intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent, produced an average increase in blood pressure of 11 mm. of mercury in two instances (40 per cent), whereas in three (60 per cent), there was no change in blood pressure (table 5).

TABLE 5.—*Combinations of Sodium, Calcium and Potassium Chloride*

	Sodium Chloride, 20% Calcium Chloride, 0.5%			Sodium Chloride, 20% Calcium Chloride, 5%			Sodium Chloride, 20% Potassium Chloride, 0.5%		
	Total Observation	48 Hr. Ob- struc- tion	72 Hr. Ob- struc- tion	Total Observation	48 Hr. Ob- struc- tion	72 Hr. Ob- struc- tion	Total Observation	48 Hr. Ob- struc- tion	72 Hr. Ob- struc- tion
Number of observations.....	5	3	2	4	..	..	6	3	3
Average dose per Kg. of body weight, cc.....	2.2	1.5	3.3	2.7	2.7	..	3.6	3.5	4.1
Average blood chloride before, mg. per 100 cc..	641.5	641.5	..	616.2	616.2	..	619.1	639	578.3
Average blood chloride after, mg. per 100 cc...	788.5	788.5	..	816	816	..	793.6	802.3	785
Increase in blood chloride, per cent.....	22.6	22.6	..	32.5	32.5	..	21.1	21.6	35.8
Increased intestinal activity, per cent.....	100	100	100	100	100	..	83.3	100	66
No change in intestinal activity, per cent.....	0	0	0	0	0	..	16.6	0	33
Decreased intestinal activity.....	0	0	0	0	0	..	0	0	0
Average increase in tone, mm.....	73.8	74.6	72.5	25.7	25.7	..	58.8	78.6	29
Average increase in amplitude, mm.....	16.6	14	20	12.5	12.5	..	19.4	26.6	8.5
Average duration of in- creased activity, min..	19.2	19	19	17.2	17.2	..	19.4	17	23

#### SODIUM CHLORIDE, 20 PER CENT; POTASSIUM CHLORIDE, 0.5 PER CENT

The effect of the intravenous administration of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent, on animals with forty-eight hour and seventy-two hour intestinal obstruction was determined in six instances. The amounts injected varied from 1.5 to 10.3 cc. with an average of 3.6 cc. per kilogram of body weight. The average blood chloride values before and after the administration of the hypertonic salt solution were 619.1 and 793.6 mg., respectively, an average percentage increase of 21.1. In all but one of the six instances (83.3 per cent) there were increases in intestinal activity. In the five in which there was an increased intestinal activity, the average increase in intestinal tone and amplitude were 58.8 and 19.4 mm., respectively.

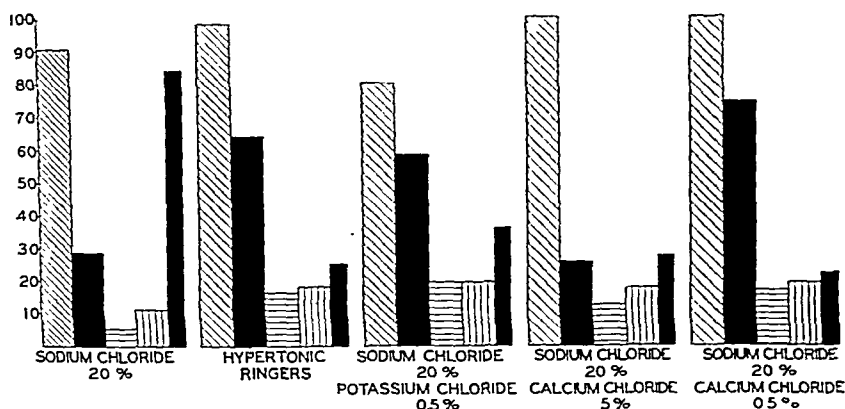


Fig. 17.—Graphic representation comparing the effects on intestinal activity of the intravenous administration of sodium chloride, 20 per cent, of a hypertonic Ringer's solution, of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent, of sodium chloride, 20 per cent, and calcium chloride, 5 per cent, and of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. The hypertonic Ringer's solution produced a more marked increase in intestinal activity as regards increases in tone and amplitude and duration of activity than did sodium chloride, 20 per cent. Sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent, was more efficacious in stimulating intestinal activity than sodium chloride, 20 per cent, and calcium chloride, 5 per cent, and also sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent. The addition of potassium and calcium to sodium chloride increased the stimulating properties of the sodium chloride.

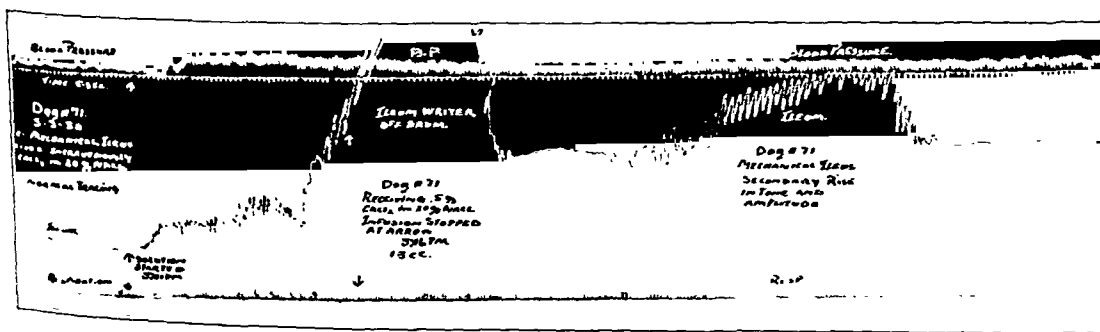


Fig. 18.—Kymographic tracing showing the effect on forty-eight hour obstructed intestine of the intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. Almost immediately after the beginning of the infusion, there was a slight rise in intestinal tone associated with an increase in intestinal movement. After approximately one and one-half minutes, there was a sudden rise in intestinal tone which was so great that the writing lever passed off the kymographic drum. This was followed by an increased tone with a little movement, following which there was another period of increased activity consisting of an increase in intestinal tone and amplitude of intestinal movement (open abdomen technic).

The average duration of the increased activity was 19.4 minutes (figs. 17 and 20). In three animals with forty-eight hour obstruction, the average dose per kilogram of body weight was 3.5 cc. The average blood chloride values before and after the administration of the hypertonic salt solution were 659 and 802.3 mg., respectively, a percentage increase of 21.6. All of this group (100 per cent) showed increases

Fig. 19.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. There was a sudden rise in intestinal tone associated with a very marked increase in intestinal movement. This persisted for a relatively long period of time (open abdomen technic).

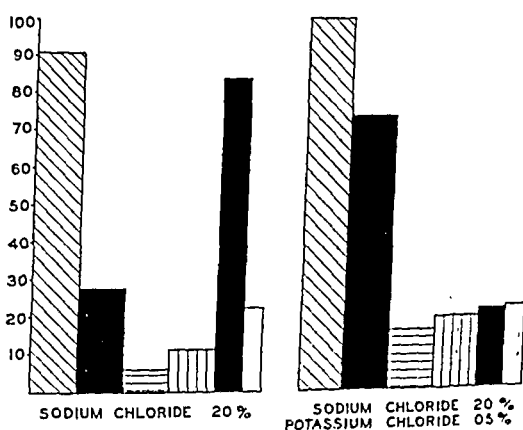


Fig. 20.—Comparison of the effect on intestinal activity of the intravenous administration of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent. There was a greater percentage of increase in intestinal activity following the administration of the latter solution than following the administration of the former. The increases in intestinal tone and amplitude of intestinal movement were also greater.

in intestinal activity with an average increase in tone and amplitude of 78.6 and 26.6 mm., respectively (fig. 21). The average duration of the increased activity was seventeen minutes. In the three animals with seventy-two hour obstruction, the average amount injected per kilogram

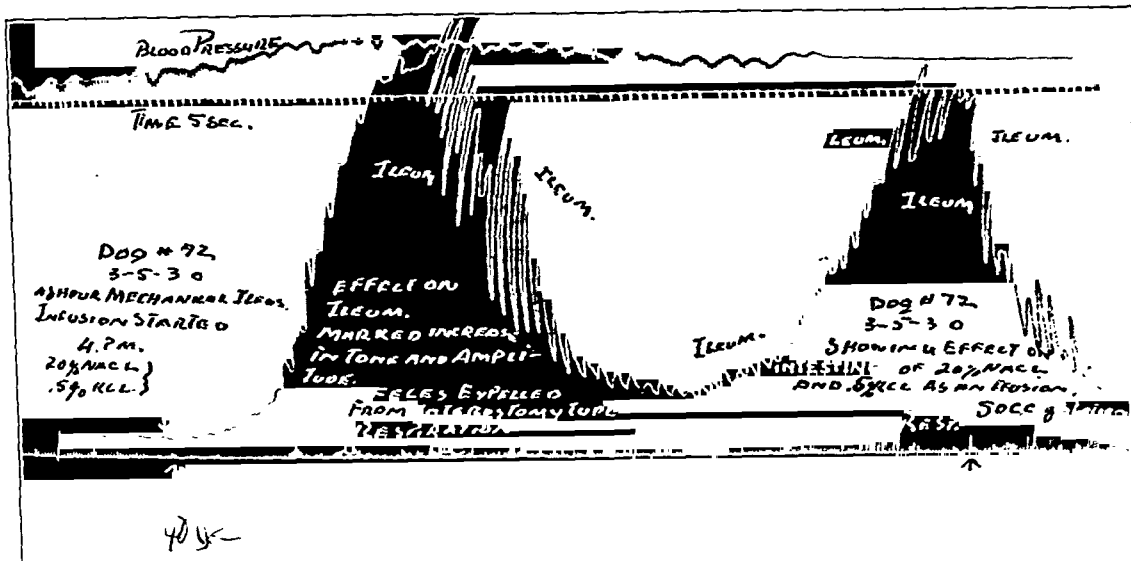


Fig. 21.—Kymographic tracing showing the effect on forty-eight hour obstructed intestine of the intravenous administration of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent. There occurred a marked increase in intestinal activity as evidenced by periodic increases in intestinal tone and amplitude of intestinal movement (open abdomen technic).



Fig. 22.—Kymographic tracing showing the effect on seventy-two hour obstructed intestine of the intravenous administration of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent. There occurred first an increase in intestinal movement associated with a relatively slight rise in intestinal tone. This, however, was followed by periodic increases in intestinal tone and amplitude (open abdomen technic).

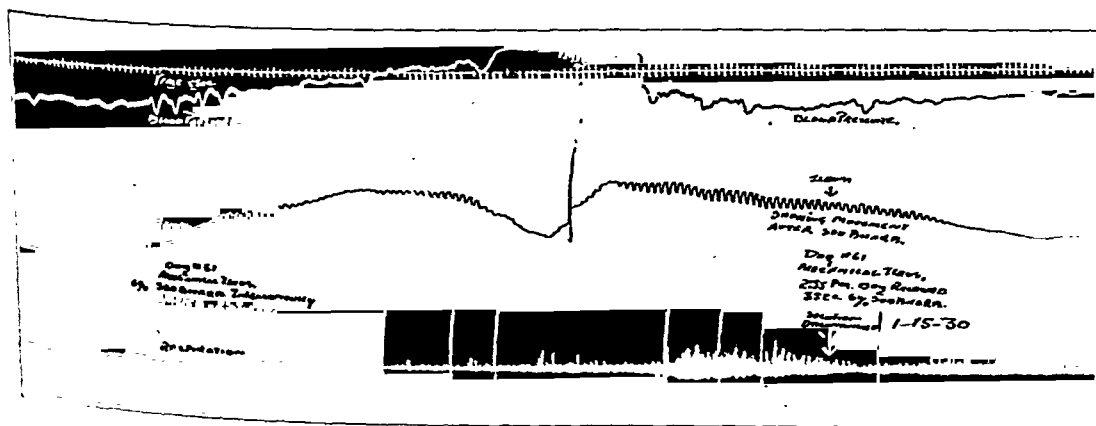


Fig. 23.—Kymographic tracing showing the effect on forty-eight hour obstruction of the intravenous administration of sodium bicarbonate, 6 per cent. Almost immediately after the beginning of the infusion, there was an increase in intestinal activity as evidenced by a rise in intestinal tone and also an increase in the amplitude of intestinal movement (open abdomen technic).

of body weight was 4.1 cc. The average blood chloride values before and after the intravenous administration were 578.3 and 785 mg., respectively, a percentage increase of 35.8. Only two (66 per cent) of these three showed an increased intestinal activity, whereas one (33 per cent) showed no change in the activity. In the two in which there was an increase in intestinal activity, the average increases in tone and amplitude were 29 and 8.5 mm., respectively (fig. 22). The average duration of the increased activity was twenty-three minutes. In only five of the six instances in which sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent, were used were blood pressure determinations made. In two (40 per cent), there was an average increase in blood pressure of 9 mm. of mercury. In two (40 per cent), there was no change in blood pressure, whereas in one, the carotid cannula clotted, so that the blood pressure could not be determined (table 5).

#### COMMENT

The advisability of administering chloride solutions to subjects with intestinal obstruction is now well appreciated, largely due to the investigations of Haden and Orr,<sup>11</sup> who showed that in high intestinal obstruction, at least, there almost invariably occurs a hypochloremia and an associated alkalosis. Raine and Perry<sup>12</sup> demonstrated that if a low intestinal obstruction persists long enough, a hypochloremia will also develop as in high obstructions. Clinically, chlorides have been administered largely in the form of physiologic or slightly hypertonic (1, 2 or 3 per cent) sodium chloride solutions, primarily for the purpose of combating the existing hypochloremia. Contrary to the negative results obtained by Hughson and Scarff<sup>1</sup> and Orr<sup>4</sup> with a physiologic sodium chloride solution, we have obtained an increased intestinal activity in 50 per cent of our observations made following the intravenous injection of a physiologic Ringer's solution (fig. 11). This reaction was, however, much less marked than that seen following the use of hypertonic solutions.

As a result of the original observations of Hughson and Scarff<sup>1</sup> and the investigations of Ross,<sup>2a</sup> the use of hypertonic sodium chloride solutions in the cases of adynamic ileus has become quite popular and

11. Haden, R. L., and Orr, T. G.: Chemical Changes in Blood After Intestinal Obstruction, *J. Exper. Med.* **27**:365, 1923; Effect of Sodium Chloride on Chemical Changes in Blood of Dog After Pyloric and Intestinal Obstruction, *ibid.* **38**:55, 1923; Effect of Inorganic Salts on Chemical Changes in Blood of Dog After Obstruction of Duodenum, *ibid.* **39**:321, 1924; Experimental High Intestinal Obstruction in the Monkey, *ibid.* **41**:107, 1925; Obstruction of the Jejunum: Effect of Sodium Chloride on Chemical Changes in Blood of Dog, *Arch. Surg.* **11**:859 (Dec.) 1925.

12. Raine, F., and Perry, M. C.: Intestinal Obstruction: Experimental Studies on Toxicity, Intra-Intestinal Pressure and Chloride Therapy, *Arch. Surg.* **19**:478 (Sept.) 1929.

in many instances life-saving. The exact mechanism by which hypertonic salt solutions stimulate intestinal activity is not known. Hughson and Scarff<sup>1</sup> showed that resection of the splanchnic and vagus nerves caused no alteration in the response of the intestine to hypertonic sodium chloride solutions. They also obtained no change in the response following the painting of a loop of intestine with 5 per cent procaine hydrochloride or 1:1,000 nicotine solution. A characteristic response was not obtained only when the blood supply to the loop of intestine was markedly interfered with. Bouisset and Fabre,<sup>13</sup> as a result of their experimentation, concluded that hypertonic salt solutions, by inhibiting the splanchnic effect, remove the inhibition exerted on the intestine by the splanchnics. They found the characteristic inhibition of intestinal activity following splanchnic stimulation could be prevented by the intravenous administration of hypertonic salt solution.

Dehydration of the organism resulting from the injection of the hypertonic solution cannot be the cause of the reaction, because we<sup>14</sup> have shown that the intravenous administration of a hypertonic dextrose solution invariably inhibits rather than stimulates intestinal activity. Hammett,<sup>15</sup> working with an isolated duodenal segment of the albino rat, found that the addition of sodium carbonate or sodium hydroxide to the surrounding fluid caused a contraction of the intestinal musculature. King and Church,<sup>16</sup> working with intact animals, found that the intravenous injection of sodium bicarbonate increased the intestinal activity. Dreyer and Tsung<sup>2j</sup> found that an increased intestinal activity occurred following the intravenous injection of hypertonic solutions of sodium chloride, sodium sulphate, sodium bicarbonate and sodium carbonate. We have also been able to corroborate the finding that the intravenous injection of a hypertonic sodium bicarbonate solution caused an increase in intestinal activity (fig. 23). Hammett<sup>16</sup> expressed the belief that increased intestinal activity is the result of an increase in the hydroxyl ions and that relaxation occurs whenever there is an excess of hydrogen ions. King and Church<sup>16</sup> are also of this opinion. That the reaction is not due to the disturbance in the sodium-calcium balance is indicated by King and Church's results, in which they were unable to influence the reactions produced by the injection of sodium

13. Bouisset, L., and Fabre, P.: Action of Hypertonic Sodium Chloride on Extrinsic Innervation: Effects on Sympathetic, *Compt. rend. Soc. de biol.* **107**: 688, 1931.

14. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Effect of Insulin and Glucose on Normal and Obstructed Intestine, *Proc. Soc. Exper. Biol. & Med.* **29**:264, 1931.

15. Hammett, F. S.: Rôle of Change in Hydrogen-Ion Concentration in Motor Activity of Small Intestine, *Am. J. Physiol.* **60**:52, 1922.

16. King, C. E., and Church, J. G.: Motor Reaction of Muscularis Mucosae to Some Drugs, *Am. J. Physiol.* **66**:428, 1923.

bicarbonate by injecting soluble calcium salts. It is difficult to interpret the results which we have obtained following the intravenous injection of hypertonic salt solutions in view of the findings of these investigators, because even though the determination of the carbon dioxide-combining power of the plasma was not made, it is probable that in some of the animals, at least, there existed some degree of alkalosis. If such were present, the administration of hypertonic salt solution should, according to Hammett's and to King and Church's investigations, by decreasing the hydroxyl ions, actually produce a decrease in intestinal movement.

The present study confirms the previous experimental and clinical investigations as regards the stimulating effects of 20 per cent sodium chloride on obstructed bowel. We believe that we have also demonstrated, at least on the experimental animal with obstruction, that the use of hypertonic solutions containing other salts besides sodium chloride are more efficacious than the use of sodium chloride solutions alone. In considering our results, it is probably necessary to differentiate the results obtained in the experiments in which the open abdomen technic was used from those obtained in experiments in which the closed abdomen technic was used. The hypertonic Ringer's solution was used both in open abdomen and in closed abdomen experiments. The results obtained are not exactly comparable because the amounts of solution used in the open abdomen experiments (average 2.5 cc. per kilogram of body weight) were more than twice as large as the amounts employed in the closed abdomen experiments (average 1.17 cc. per kilogram of body weight). However, the response of the intestine to the intravenous injection of hypertonic salt solutions with the former was so much greater than with the latter that one is probably justified in assuming that the more marked results obtained with the former are at least in part due to the type of technic employed. There was an increased intestinal activity following the intravenous injection of the hypertonic Ringer's solution in 97.3 per cent of the open abdomen experiments and in 94.7 per cent of the closed abdomen experiments, which difference we believe can be disregarded. However, the average increases in tone in the open abdomen and the closed abdomen experiments were 61.2 and 16.1 mm., respectively. The increases in amplitude were 18.4 and 2.9 mm., respectively. The duration of this increased activity (17.6 minutes) was the same in both experiments. Even though larger amounts of the hypertonic Ringer's solution were used in the open abdomen experiments, the average percentage increase in blood chlorides was 22.5 as compared with 23.7 in the closed abdomen experiments. This was because the average normal blood chlorides before the intravenous administration of the hypertonic Ringer's solution was less in the closed abdomen experiments than in the open abdomen experiments. It is, therefore, obvious that a comparison of the results obtained

following the intravenous administration of hypertonic salt solutions should be made only when the same type of experiment is employed. Comparing the results obtained following the intravenous administration of 20 per cent sodium chloride solution in the animals with forty-eight and seventy-two hour obstruction with those obtained following the intravenous administration of the hypertonic Ringer's solution, both experiments being performed according to the open abdomen technic, considerable difference is noted (fig. 2). In spite of a much larger dose in the former instance (an average of 8.4 cc. per kilogram of body weight as compared with 2.5 cc. in the latter), in only 90.4 per cent was there an increase in intestinal activity as compared with 97.3 per cent when the hypertonic Ringer's solution was employed. In 4.4 per cent of the former group, there was no change in intestinal activity and in 4.4 per cent, there was an actual decrease. More significant are the changes in the tone and amplitude. The increases in tone obtained by the intravenous administration of the hypertonic sodium chloride solution and the hypertonic Ringer's solution were 28.6 and 61.2 mm., respectively. The average increases in amplitude were 5.05 and 18.4 mm., respectively. The average durations of the increased activities were 11.1 and 17.5 minutes, respectively. It is thus evident from these observations that the intravenous administration of a hypertonic Ringer's solution is more efficacious (even though much smaller doses are employed) in stimulating the intestinal musculature in the presence of obstruction than is a hypertonic sodium chloride solution.

By comparing the results obtained following the intravenous administration of a hypertonic Ringer's solution with those obtained following the intravenous administration of a Hartmann's "hypertonic" combined solution (the closed abdomen technic was used in both), the following was noted (fig. 7): In both experiments the dose was practically the same (1.17 cc. of Ringer's solution and 1.16 cc. per kilogram of body weight of Hartmann's solution). In both groups, there were approximately the same percentage increases in intestinal activity. However, there was some difference in the character of the response of the intestine to the intravenous administration to the hypertonic solutions. The average increases in tone following the administration of hypertonic Hartmann's solution and Ringer's solution were 20 and 13.1 mm., respectively, whereas the increases in amplitude were 3.6 and 2.9 mm., respectively. The durations of the increased activities were 20.2 and 17.6 minutes, respectively. One would expect little difference in reaction of the intestine to these two hypertonic solutions because of their similarity. The hypertonic Ringer's solution as employed contains 18 per cent sodium chloride as compared with 11.7 per cent in the hypertonic Hartmann's solution. Sodium lactate, 5.6 per cent, is contained in the hypertonic Hartmann's solution but not in the hypertonic Ringer's



solution. Potassium chloride contents in the hypertonic Ringer's and the Hartmann's solution are 0.6 and 0.7 per cent, respectively. The calcium chloride contents were practically the same, 0.52 per cent in the hypertonic Ringer's solution and 0.54 per cent in the hypertonic Hartmann's solution. The principal differences are that there is a higher concentration of sodium chloride in the hypertonic Ringer's solution, and the hypertonic Hartmann's solution contains sodium lactate.

It is apparent that the administration of other salts besides sodium chloride is of value in stimulating the intestine. Whitehead<sup>17</sup> found, working with ileal and jejunal segments employing the Magnus technic, that the addition of calcium and potassium to the solution in amounts exceeding isotonicity caused a progressive increase in tone and a decrease in amplitude. In our intact animal experiments, we found not only a much more marked increase in tone in the animals receiving the hypertonic Ringer's solution, but also a materially increased amplitude. The duration of the increased activity was greater in the animals receiving the hypertonic Ringer's solution.

The relative effects of the addition of calcium and of potassium to sodium chloride solutions were also determined in the present investigation. However, the number of observations made following the intravenous administration of each is so small that few or no positive deductions can be made. The effect of sodium chloride, 20 per cent, and calcium chloride, 5 per cent, in forty-eight hour obstructed intestine was determined in four instances. In all instances, there was an increase in intestinal activity. Similar results were obtained by the intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. In five observations, the character of the reaction obtained was much more marked than that obtained with a higher concentration of calcium chloride. The average increase in tone following the intravenous administration of sodium chloride, 20 per cent, and calcium chloride, 5 per cent, was 25.7 mm. as compared with 73.8 mm. increase in tone from the intravenous injection of sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. The average increases in amplitude were 12.5 and 16.6 mm., respectively. The average durations of the increased activities were 17.2 and 19.2 minutes, respectively. That the addition of calcium chloride to a hypertonic sodium chloride solution enhances the value of the solution as an intestinal stimulant is evidenced by the difference in the results obtained by sodium chloride, 20 per cent, alone and sodium chloride, 20 per cent, combined with calcium chloride, 0.5 per cent (fig. 17). This difference was especially marked in the animals with forty-eight hour obstructions. Intestinal activity was increased 94.1 per cent. It was increased 100 per cent in

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17. Whitehead, R. W.: Responses of Excised Intestines to Alterations of Electrotype Concentrations (Na, Ca, K), *Am. J. Physiol.* **89**:253, 1929.

the animals with forty-eight hour obstruction receiving sodium chloride, 20 per cent, and sodium chloride, 20 per cent, combined with calcium chloride, 0.5 per cent, respectively. The average increases in tone were 20.5 and 74.6 mm., respectively, and the average increases in amplitude were 2.25 and 14 mm., respectively. The average duration of the increased activities were five and nineteen minutes, respectively. A comparison of the results obtained by the two hypertonic solutions is not free from criticism, because even though in each the open abdomen technic was used, the number of observations is not the same. Twenty-one observations were made with sodium chloride, 20 per cent, whereas only five were made with sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. Whitehead<sup>17</sup> found that the addition of calcium alone to the perfusing fluid in his investigations with ileal and jejunal muscle strips caused an increase in rate and tone and a decrease in amplitude as the concentration of calcium was increased above isotonicity. We found also an increase in amplitude as well as an increase in tone, but little change in rate (figs. 18 and 19). Whitehead<sup>17</sup> also observed that periodicity occurred when calcium was added to the solution, which was also evident in our experiments (fig. 18). The addition of calcium chloride, 0.5 per cent, to the sodium chloride, 20 per cent, had a more markedly stimulating effect on the intestine than the addition of calcium chloride, 5 per cent. It is possible that the excessive amounts of calcium chloride present in the 5 per cent solution may have exerted an inhibitory effect on the musculature of the intestine, as suggested by the investigations of Kennedy,<sup>18</sup> Bauer, Salter and Aub,<sup>19</sup> and Alvarez.<sup>20</sup> In subsequent experiments, Fitzhugh, Miller, Taylor and Aub<sup>21</sup> were unable to show experimentally that calcium, even in high concentrations, decreased the intestinal activity.

Rather interesting results were obtained following the intravenous administration of sodium chloride, 20 per cent, and potassium chloride, 0.5 per cent. The dose employed was relatively large, 4.6 cc. per kilogram of body weight as compared with 2.2 cc. in the group receiving sodium chloride, 20 per cent, and calcium chloride, 0.5 per cent. There was considerable difference in the response to the two solutions.

18. Kennedy, W. P.: Normal Response of the Isolated Uterus and the Response After Experimental Interference, *Quart. J. Exper. Physiol.* **16**:332, 1927.

19. Bauer, Walter; Salter W. T., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism, Xa: The Use of Calcium Chloride to Relieve Peristaltic Pain, *J. A. M. A.* **96**:1216 (April 11) 1931.

20. Alvarez, W. C.: Influence of Drugs on Intestinal Rhythmicity, *Am. J. Physiol.* **46**:554, 1918.

21. Fitzhugh, Greene; Miller, M. L.; Taylor, G. W., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism, Xb: The Effect of Intravenous Calcium Chloride on Peristalsis Following Intestinal Obstruction in Dogs, *Am. J. Physiol.* **97**:142, 1931.

Whereas in the group receiving the solution containing calcium chloride there was stimulation in the intestine in all (100 per cent), in the group receiving the solution containing potassium chloride, there was stimulation of the intestine in only 83.3 per cent. The increases in tone in the groups receiving calcium chloride and potassium chloride were 73.8 and 59.8 mm., respectively. The increases in amplitude were 16.6 and 19.4 mm., respectively. The durations of these increased activities were 19.2 and 19.4 minutes, respectively. It is thus apparent, if one is justified in comparing the results obtained in the relatively small group of experiments in which potassium was added to the sodium chloride, that the addition of potassium to the hypertonic sodium chloride solution is efficacious in stimulating the intestine. Whitehead<sup>17</sup> found following the removal of potassium from the perfusion fluid in the Magnus preparation that the restoration of the potassium always resulted in a characteristic temporary inhibition of the activity of the intestinal musculature. However, the addition of potassium above normal resulted in a progressive rise in tonus and a characteristic periodicity, which was also evident in our experiments (fig. 21). Alvarez<sup>20</sup> also showed that the addition of potassium salts increased the tone and amplitude of intestinal movement. It is apparent from our investigations that in the experimental animal, at least, the administration of calcium and potassium to sodium chloride is of advantage in stimulating the intestine in the presence of obstruction, as the intravenous injection of the hypertonic Ringer's and hypertonic Hartmann's solutions were more efficacious than the intravenous injection of the hypertonic sodium chloride solution alone.

We have used the hypertonic Ringer's solution clinically with very gratifying results and feel, on the basis of our experimental observations and our clinical results, that its use is justified. In the clinic, we have employed from 10 to 15 cc. of the 20 per cent Ringer's solution or the Hartmann's solution prepared in the way described. It is extremely important that this solution be given slowly, not faster than 1 cc. per minute, in order to obviate any danger of sodium poisoning. Within a short time after the intravenous administration, a rectal tube should be introduced, and if no results are obtained, an enema should be given because frequently an emptying of the small bowel into the colon occurs without defecation. Probably the greatest danger from the use of hypertonic salt solution is the increased coagulability of the blood, which danger, however, can be obviated by using amounts not greater than 10 to 15 cc. and injecting the solution slowly. We have repeated the injection as often as every eight hours and feel that such a procedure is justified in those cases in which normal reestablishment of intestinal movement has not occurred.

# PERINEAL PROSTATECTOMY

## PRESENTATION OF THE WILDBOLZ TECHNIC

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LOS ANGELES

The controversy concerning the relative merits of the perineal and suprapubic routes of prostatectomy has finally become somewhat stabilized. Successful results in prostatectomy depend on the method in which the surgeon is trained and on variables of the individual case.

The method of suprapubic prostatectomy has been to a great extent standardized. However, the perineal route has not as yet reached full maturity, and in its growth has been wont to arouse the concern of many of its benefactors. The numerous approaches and modifications, many of which have been put forth by foreign contributors, have left many groping for the most proficient and efficacious route.

The medical profession owes much to Young and his pioneer work in standardizing a perineal route, and to the work subsequently carried on by his pupils. However, in order to establish a final clarity, the various methods should be put forth and clearly stated.

The methods of perineal approach may be briefly summarized as:

- I. Median transurethral methods
  1. Berndt
  2. Praetorius
  3. Alexander
  4. Syms
  5. Goodfellow
- II. Ischiorectal method of Voelcker
- III. Wilm's lateral approach
- IV. Anatomic conservation by surgical dissection of perineum
  1. Zuckerkandl
  2. Proust
  3. Young's operation and modifications
    - (a) Geraghty
    - (b) Transprostatic en masse enucleation
    - (c) Complete extracapsular prostatoseminal vesiculectomy for cases of pure hyperplasia with pronounced infection and vesiculitis
  4. The Wildbolz method

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While working with Professor Voelcker at Halle, Germany, I had the chance to help in performing and later to perform his ischiorectal prostatectomy. In other European clinics, namely, in Berlin with Prof. A. von Lichtenberg at the St. Hedwig's Krankenhaus, and in Berne, Switzerland with Prof. Hans Wildbolz at the Chirurgische Klinik am Inselspital, other methods of perineal prostatectomy were used which afforded me the opportunity to make a comparative study of the various methods.

With the cooperation of Professor Wildbolz, I have the opportunity to present to American literature the illustrated technic of the Wildbolz method of perineal prostatectomy. Possessing a working acquaintance with the Young method and its modifications, as well as the German methods of Voelcker, Wilms, Zuckerkandl and others, I am presenting this paper as a comparative study to clarify the various methods of perineal approach, as well as to present the Wildbolz method.

In the various methods of perineal prostatectomy used in America, the most conspicuous disadvantage is the possible occurrence of postoperative incontinence. To some surgeons this factor always looms as an obstacle in adopting the perineal method as a routine. It became necessary, therefore, for some one to modify the technic so as to avoid this possibility. The Wildbolz method overcomes postoperative incontinence by not exposing, opening or disturbing the membranous urethra and its musculature. Moreover, in that it is a purely intracapsular enucleation of the adenomas, both urinary sphincters are carefully preserved.

The entire urethral musculature, as emphasized by Schwarz, must be considered as a single functional unit. However, of the whole urethral unit, the external and internal sphincters are the most important. The reliability of urinary control is directly dependent on the intactness of the external sphincter. Further, in the mechanism of urinary control, the internal sphincter plays a lesser rôle than the external sphincter. However, the internal sphincter can at times act to produce a watertight exit, as exemplified in cystograms.

This was also observed clinically by Wildbolz in patients during the first days following perineal prostatectomy, when they were left without retention catheters. The bladder would arbitrarily empty itself through the perineal wound, but between micturitions, the wound, although lying in front of the internal sphincter, remained dry.

The events that occur during the normal ejaculation of semen show how completely the internal sphincter can control the urinary flow. During the act of ejaculation the external sphincter opens completely, and yet not a drop of urine flows out, thus showing that the

internal sphincter can withhold the urine in the bladder without the aid of the external sphincter.

As depicted, the internal sphincter is quite important, but hardly the main factor in urinary control as many have tried to maintain. If this were true, some bladder incontinence should more frequently occur following suprapubic prostatectomy in which the internal sphincter is frequently greatly dilated, at times even torn. These facts were also borne out by Illyés, who noted by urethroscopic examination, following suprapubic prostatectomy, that a functional loss of the internal sphincter occurred.

Other evidence to verify the lesser importance of the internal sphincter as compared to the external sphincter is presented by the catheter test of Finger and Wildbolz; namely, that a catheter passed just beyond the external sphincter into the posterior urethra will drain the contents of the bladder without any strangury, but as soon as the catheter is pulled distal to the external sphincter, the urinary flow will cease.

It becomes obvious that the internal sphincter should by all means be protected during prostatectomy, but, even more important, it is necessary to maintain an intact external sphincter so as to have a watertight control of the bladder following the procedure. It is the preservation of the external sphincter which is not given sufficient attention in most of the present day methods of perineal prostatectomy.

In the method of Albarran and Proust, which was the first most commonly used, the prostatic capsule was split in its entire length from the membranous portion of the urethra to the neck of the bladder, and on account of this the external sphincter was necessarily injured. The instruction of Young to insert the retractor through the membranous portion of the urethra also led unavoidably to an injury of the external sphincter. This is further exemplified in the recommendation of Berndt and Praetorius to split the external sphincter as a routine in their method, the so-called median perineal prostatectomy. It is obvious that by such procedure, urinary control would be frequently made uncertain. Even Zuckerkindl, with whom Wildbolz most nearly agrees, did not attach sufficient importance to the external sphincter, in that he split the prostatic capsule too far distally. He began the capsular incision at the root of the membranous portion of the urethra and carried it very far proximally onto the prostatic capsule. Zuckerkindl realized that this constituted a weak spot in his method, as was brought out by the following words: "By this method one succeeds in isolating the urethra to a greater extent than is possible by the Freyer operation, inasmuch as the cuticular portion is also loosened from its surroundings."

The main goal in developing the Wildbolz method of perineal prostatectomy is to preserve the external sphincter in its entire function in

spite of the complete enucleation of the prostate; therefore, any preparation or exposure of the membranous urethra is avoided. It is planned to leave this portion of the urethra and its enveloping external sphincter completely undisturbed and uninjured and out of the field of operation. In order to accomplish this and to preserve all the muscular bundles of the external sphincter which encircle the prostatic portion, the capsular incision is placed as far as possible toward the bladder. The external sphincter is composed not only of encircling striated muscle enervated by the pudendic nerve, but also of smooth muscle enervated by the autonomic nerves. These muscle bundles extend on to the apex of the prostate. The Wildbolz prostatic capsular incision was therefore chosen to allow this important muscle ring and its extension on to the prostate to remain intact.

It is quite unimportant as to whether or not the ejaculatory ducts are patent following the operation, because the routine bilateral vasotomy, either before or at the time of operation, disturbs the patency of the seminal passages. Potency does not depend so much on the patency of the ejaculatory ducts as on the complete preservation of the nerves approaching the prostate gland.

Wildbolz stated:

That the difference of incision between Zuckerkandl and myself is not unimportant as regards efficient urinary control is shown by the fact that Zuckerkandl has not used his method very often on account of the frequency of postoperative incontinence, and therefore, he usually prefers the supra-pubic method; whereas with my method, I have obtained such good results that for 20 years I have continued to use the perineal prostatectomy and consider it the method of choice. To him who doubts the good bladder control following my operation, I wish to give this thought, namely, that if my patients had an unsatisfactory urinary control following the operation, they would have influenced other prospective patients to avoid prostatectomy at my hands, and would have sought the help of other surgeons who use the supra-pubic method; because it is well known that a surgeon's failures become known more quickly amongst his colleagues and hospital circles than his successes.

#### TECHNIC

The operation is almost always carried out with sacral anesthesia. In less than 10 per cent of the cases in which local anesthesia does not work completely, or due to hyperanxiety of the patient, ether anesthesia is used. The patient is placed in an exaggerated lithotomy position, with the thighs sharply flexed against the abdomen, so that the perineum is completely exposed and tense. A metal catheter is passed by way of the urethra into the bladder and left in place.

The operation begins with the semicircular perineal incision of Zuckerkandl, which extends from one ischial tuberosity to the other, with the convexity toward the scrotum, about a thumb's thickness below the dorsal edge of the bulb. After splitting the subcutaneous fat and the superficial perineal fascia, one is able to discern the bulbous raphe in the middle of the wound by a light dorsal pull on the undersurface of the wound. With short sharp incisions made close to the

raphe of the bulb, the posterior end of the urethral bulb is dissected out. This is made easier by means of blunt dissection of the fatty tissue hanging on to the sides of the bulb, after which the bulb will clearly protrude into the wound. The lateral portions of the perineal incision should not be cut too deeply so as not to injure the branches of the pudendic nerve which supply the external sphincter. Following the dissection of the posterior bulbous end, the patient is frequently placed in a semi-Trendelenburg position. This is done so that during the following dissection around the posterior end of the bulb the light may be thrown into the depths of the wound, in order that the recto-urethral muscle extending posterior to the bulb may be clearly seen.

By pulling down the posterior edge of the wound with a flat retractor, or even better by means of the fingers, the rectum and recto-urethral muscle will be put on a stretch. In order to avoid any danger of a rectal injury, the recto-urethral muscle must be sharply divided near the urethral bulb (fig. 1). After this muscle is cut through, the rectum and levator ani will fall posteriorly, and the bulbous

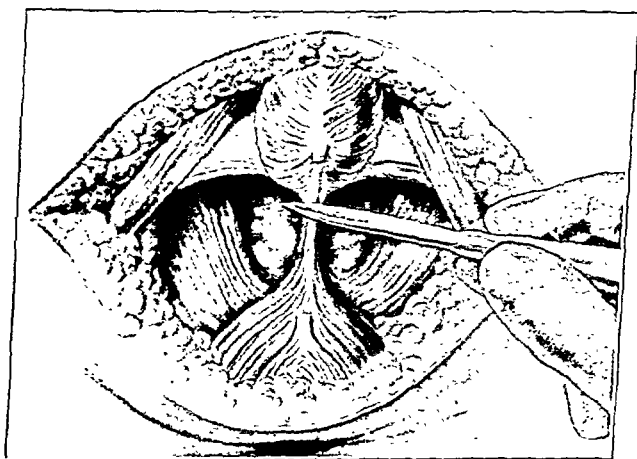


Fig. 1.—The perineal incision has been made, the muscles exposed, and the recto-urethral muscle is being severed near the urethral bulb. (The illustrations in this article are from the monograph of Hans Wildbolz: *Technik der perinealen Prostatektomie*, Urologische Chirurgie, Berlin, Julius Springer, 1929.)

urethra and superficial transverse perineal muscles will remain anteriorly. The approach to the posterior aspect of the prostate will now be free. When the metal catheter that has been lying in the urethra is grasped and the prostate pushed prominently into the wound, the posterior aspect of the prostate, even though not immediately visible, will be easily palpable. Thus a straight line of direction from the perineal wound direct onto the prostate may be followed. The connective tissue layer which will be found on the posterior aspect should not be split far to the front, but always toward the bladder. In this manner it is possible to make the posterior aspect of the prostatic capsule completely visible without the slightest injury. The capsule may be recognized by its shimmering whiteness and unusual tenseness. Before the capsule is split, an area no larger than the size of a quarter should be exposed, and great care should be taken not to expose the capsule to too great an extent from the fascia of Denonvieller. The exposed prostatic capsule is now split in the median line by a vertical incision.



Whether the capsule is split laterally or in a median line is apparently without great importance. The median incision is preferred because it gives equally good approach to both lateral lobes, and undoubtedly more effectively preserves the nerves that lead to the prostate both posteriorly and laterally. Of greater importance than the question of either a median or a lateral incision is the fact that the incision must begin sufficiently far beyond the external sphincter to leave the latter completely intact.

The incision into the prostatic capsule should begin as far as possible from the apex of the prostate toward the bladder, about 1.5 cm. superior to the inferior edge of the point where one begins to feel the prostatic adenoma (fig. 2). It should extend superiorly to the furrow between the prostate and seminal vesicles. The importance of commencing the capsular incision as far as possible toward the bladder from the inferior edge of the adenoma is stressed, for then the muscle ring that surrounds the membranous portion of the urethra remains intact, and

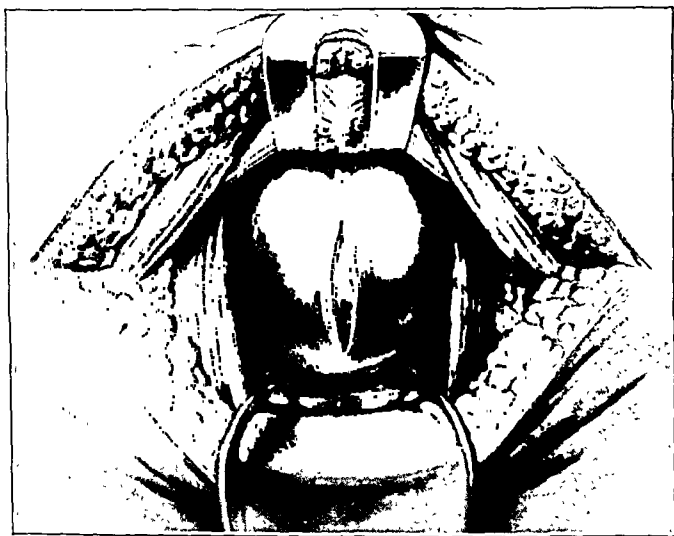


Fig. 2.—With retractors in place, the prostate and its capsule are in sight. The latter is split vertically close to the bladder.

the smooth muscle bundles of the sphincter that envelop the distal portion of the prostatic urethra are also preserved. The incision into the prostatic capsule should extend so deep into the adenoma that when the wound is separated the dividing line between the prostatic capsule and the adenoma is distinctly visible. It is not desirable at this point to cause an opening into the urethra with the initial capsular incision; however, it is not always preventable when the posterior commissure of the adenoma is very thin.

A Kocher gland enucleator is now inserted in the cleavage line between the adenoma and the prostatic capsule. As soon as a small opening is created between the capsule and the adenoma, one proceeds to enucleate the adenoma subcapsularly by means of the forefinger. During the enucleation, special care must be taken to loosen the underportion of the adenoma from the prostatic urethra as well as from the base of the bladder, so as to avoid urethral tears in either place.

After the adenoma is loosened from the prostatic capsule both posteriorly and laterally, no further enucleation is carried on until the urethra is severed as close

to the inferior end of the adenoma as possible, in order to prevent any irregular tear into the urethra or any injury to the muscle fibers of the external sphincter. This is carried out in the following manner: The index finger of the left hand is placed between the prostatic capsule and the adenoma, and the latter is pushed as far as possible toward the bladder; at the same time the urethra around it is loosened as much as possible. With the volar surface of the index finger as a guide, the urethra is cut at this point (fig. 3).

This division of the urethra is ordinarily made proximal to the colliculus seminalis, as can be verified by urethroscopic examination. The adenomatous nodules of the prostate always develop around that portion of the urethra which lies between the colliculus and the bladder, and never peripheral to the colliculus. Thus the urethra is cut close to the lower pole of the adenoma so that the colliculus will always lie distal to it, and will be preserved. This has been proved by urethroscopy, as well as in cases that have gone to autopsy.

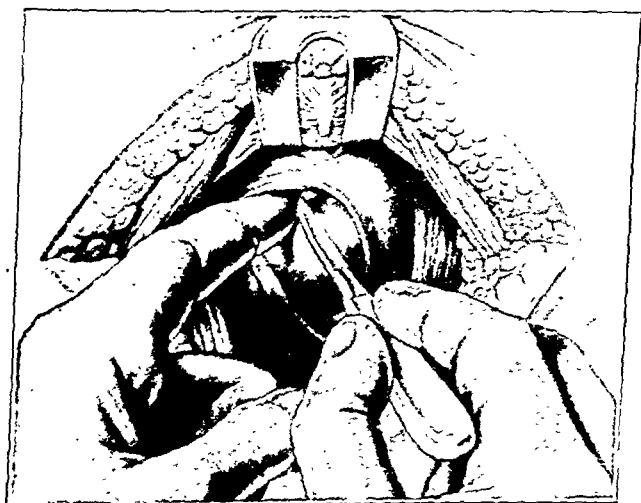


Fig. 3.—The adenoma has been loosened from the capsule and the former is pushed as far as possible toward the bladder. The urethra is severed immediately distal to the adenoma.

Following the division of the urethra at the lower pole of the prostatic adenoma, the distal portion of the prostatic urethra with the colliculus seminalis will retract anteriorly inside the prostatic capsule, and thereby escape the danger of any tears or injury which it might otherwise sustain during the following completion of the prostatic adenoma enucleation. The Young retractor is now easily inserted into the proximal portion of the urethra which is still surrounded by the prostatic adenoma. That portion of the prostate still attached to the floor of the bladder and seminal vesicles is now pulled forward into the wound and freed from the remaining attachments (fig. 4). In most cases, the adenoma will remain in one large mass, and only seldom will it fall apart into two or three nodules. After the enucleation of the prostate, a finger may be passed through the opening of the bladder which will feel like a ring, and as a rule the sphincter will contract down on the finger. It is difficult to preserve the entire intactness of the internal sphincter even by perineal prostatectomy when the adenoma has a large middle lobe which protrudes markedly into the bladder or has developed entirely intra-

vesically. During the enucleation of such a middle lobe, the internal sphincter is usually overstretched or even injured through tearing. However, only seldom is it so severely injured as to cause the opening of the neck of the bladder to gape.

With the index finger within the sphincter of the neck of the bladder as a guide, artery forceps are applied; one above, one below, one to the right and one to the left. With these four forceps, the sphincter and neck of the bladder are pulled forward into the wound, making it easier to examine the inside of the bladder with the index finger. Thus it may be definitely determined during the enucleation that no adenomatous nodules, particularly so-called middle lobe nodules, have been left at the exit of the bladder. After examining the inside of the bladder, it is thoroughly irrigated with physiologic solution of sodium chloride so as to prevent the formation of a blood clot which might later plug the retention catheter.

Following the thorough cleansing of the bladder, the opening is pulled into the wound by the four forceps, and the latter are replaced by four catgut sutures.

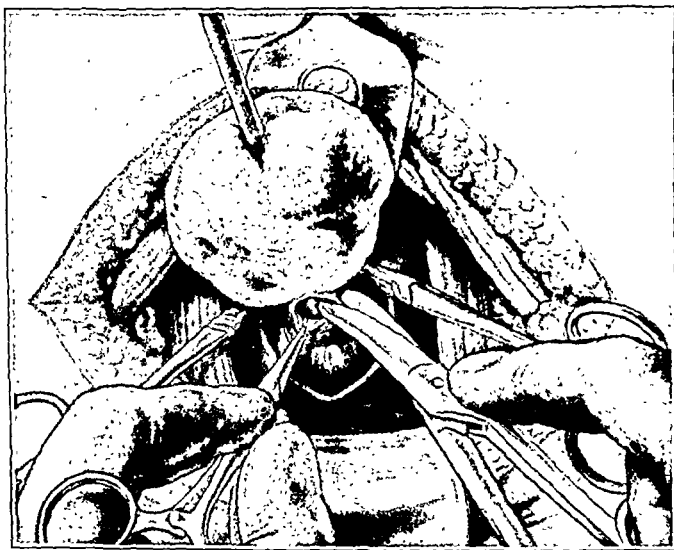


Fig. 4.—A Young retractor has been inserted into the bladder through the prostatic urethra surrounded by the adenoma, which is now pulled forward and removed by severing its remaining attachments with the bladder and seminal vesicles.

These sutures remain untied and are retained in place by clamping with forceps. So that the relation of these ligatures with the neck of the bladder may not be confused, they are fastened to the sheets, in their four respective quadrants. A metal catheter is now passed through the anterior urethra and through the operative area into the bladder. The catheter causes the distal stump of the urethra, which had retracted forward into the capsule after resection, to become clearly visible in the operative wound, and it may now easily be sutured to and with the opening of the neck of the bladder (fig. 5).

The metal catheter must be replaced by a no. 20 silk catheter before the ligatures between the neck of the bladder and the stump of the urethra are tied. Following the passage of the silk catheter, the ligatures are tied, joining the neck of the bladder and the urethra, while the catheter remains in place. The sutures joining the neck of the bladder and the urethral stump are usually sufficient to

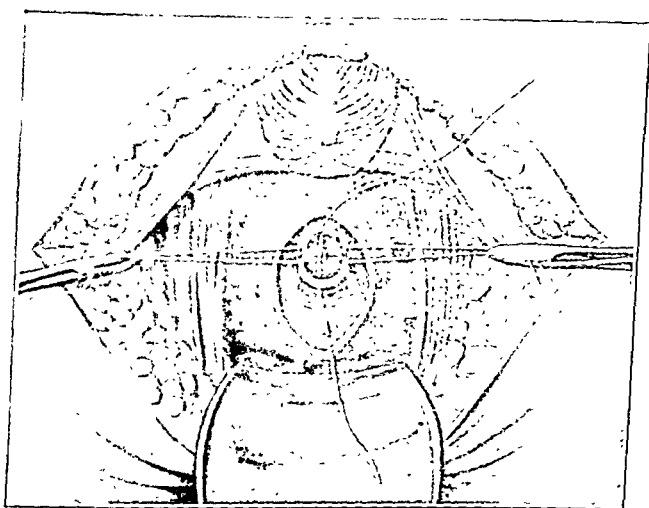


Fig. 5.—The distal and proximal ends of the urethra are united to carry out complete anatomic reconstruction.

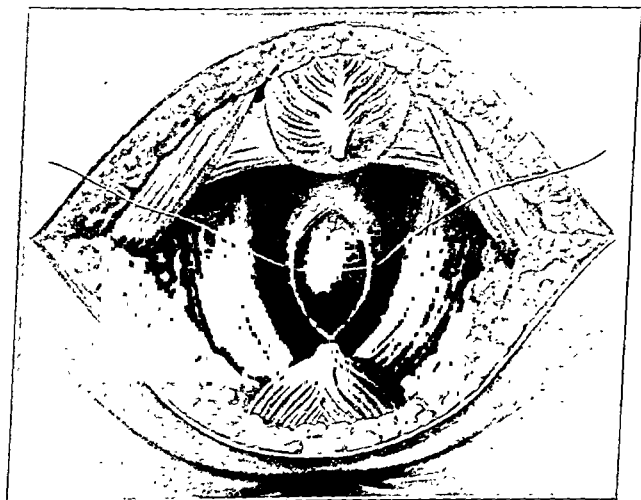


Fig. 6.—The edges of the prostatic capsule which had been split at the beginning of the operation are brought together and sutured, thus making the reconstruction complete.

control any bleeding from the edges of the urethra and bladder wounds. Only occasionally will additional sutures for hemostasis be necessary. Usually after the bladder-urethral sutures are tied, the wound will be entirely dry.

In order completely to reconstruct the anatomic relationships at the neck of the bladder, and above all to restore complete function of the muscular bundles extending on to the prostatic capsules from the external sphincter, the edges of the prostatic capsule which had been split at the beginning of the operation are now brought together and sutured (fig. 6). At this point of reconstruction, the edges are not always clearly visible in the wound, for during the enucleation of the adenoma they may have retracted laterally. They are, however, easily located, grasped with a forceps and pulled toward the middle of the wound. This lateral retraction of the prostatic capsule indicates the importance of bringing them together after the operation. Thus, by reconstruction of anatomic relationships to as nearly normal as possible, a rapid healing is promoted.

Prior to closing the perineal wound, it should be made certain that the anterior rectal wall has not been injured during the operation. A rectal examination is made and the anterior wall is pushed into the wound, so that injury, if it has occurred, can best be seen. Should the musculature be thinned in any place or the rectal mucosa injured in any way, it must be sutured and reinforced by a layer of levator ani muscle. However, where it is clear that the rectum has not been injured, such suture in the levator ani muscle is unnecessary.

Tamponage of the operative wound and drainage of the bladder through the perineal wound should not be done. Tamponage or drainage of the bladder unnecessarily delays healing of the wound by one to two weeks. To insure good drainage of any secretion, all that is necessary is the placing of a small cigaret drain into the wound extending down to, but not within, the prostatic capsule. The perineal wound should then be rather tightly closed, including skin and subcutaneous tissue, allowing only a small opening for the drain.

Prostatectomy should be immediately preceded or followed by a bilateral vasotomy, which practically always prevents a postoperative epididymitis. To undertake this vasotomy sometime before the prostatectomy in order to prevent an epididymitis during the preoperative retention catheter stage is disadvantageous. To most patients this minor procedure will appear as a major operation and will frighten them. Such a psychic strain may harm the debilitated patient almost as much as a possible epididymitis.

#### POSTOPERATIVE CARE

The perineal drain is removed three days after the operation, and the drainage canal is irrigated daily with hydrogen dioxide through a small catheter. The bladder is irrigated twice daily through the retention catheter with 1:2,000 oxyquinolin sulphate solution during the first three days and later with 1:5,000 oxy-cyanide solution.

On the third postoperative day the necessary measures to insure a bowel movement are given. From the fourth postoperative day on, the patient is allowed up daily for from two to three hours.

The retention catheter is left in place until the perineal wound is entirely closed, which usually takes from two to three weeks. A change of the retention catheter is usually unnecessary during this time; however, should it be necessary, it can easily be carried out with the help of a mandarin. It is not unusual for the perineal wound to remain entirely dry until the complete closure. There may be some drainage from the perineal wound, and it is most frequently observed between the sixth and twelfth postoperative days. Signs of inflammation in the perineal

wound hardly ever occur, even in cases in which the bladder had been infected preoperatively. Should inflammation occur, it can easily be controlled by the application of warm salicylate compresses.

## COMMENT

Rapid healing and permanent reconstruction of the bladder function is obtained by this method. In the majority of cases the operative wound closes within two weeks, and in only the very exceptional case does closure take more than three weeks. The bladder control is practically always intact. Following the removal of the retention catheter, a few patients when coughing or sneezing have temporary postoperative weakness of the sphincter muscle. Almost without exception, these symptoms of incontinence disappear after a few days. It may be stated without fear of contradiction that with this method of perineal prostatectomy one need never fear permanent postoperative incontinence.

The Wildbolz method also excludes many disadvantages of other methods of perineal prostatectomy, namely, fistulas and postoperative hemorrhage. Perineal fistulas which formerly occurred in over 7 per cent of the cases of perineal prostatectomy as shown by the accumulated literature of Pousson, no longer occur by this method of perineal prostatectomy. The perineal wound closes quickly. The occurrence of urinary fistulas is frequently mentioned in the literature as a fairly common sequela of perineal prostatectomy. This can be explained only by the fact that frequently a perineal drain is left extending all the way into the bladder.

With the Wildbolz method this complication is prevented by completely anastomosing the bladder with the urethra and placing the perineal drain to, but not into, the prostatic capsule. Experience has shown that with this technic the danger of a recto-urethral fistula is relatively small, even though its occurrence is not impossible with any method of prostatectomy.

An open incision into the rectum when exposing the prostate can definitely be prevented. However, the danger of tearing the rectum by careless handling of the perineal wound retractors is to be constantly held in mind. In order to prevent this, only very light traction should be applied to the retractor which pulls the rectum away from the operative field. Pressure against the rectum with the tip of the retractor must be particularly avoided, and the assistants must be instructed always to hold the retractor with its full flat surface against the rectal wall. Even if an open tear into the rectal wall is avoided during the course of the operation, a rectal fistula may develop. Most of these patients suffer from arteriosclerosis, so that too great exposure of the anterior rectal wall may so disturb its blood supply that secondary necrosis of the wall may occur. However, it is rather improbable that

such a necrosis will occur without any operative injury, particularly where there is no pressure of the perineal drain. Such a secondary necrosis of the rectal wall, according to my experience, is always a result of operative injury of the rectal musculature. As previously stated, the rectal wall should be carefully examined at the termination of the operation, and if injury is found, it is to be properly repaired.

The dangers of perineal prostatectomy which were previously so greatly feared, namely, urinary incontinence, fistulas and postoperative hemorrhage, are almost entirely eliminated by this method. Owing to these experiences, perineal prostatectomy may be more commonly utilized, because in many respects this method offers certain superior advantages over the suprapubic method, the foremost one being that it causes much less operative shock. It is true that the operative shock of suprapubic prostatectomy has been greatly decreased through the use of the two-stage operation; nevertheless, it is still greater than in perineal prostatectomy. This can be seen by observing the patient immediately after operation. The patient who has undergone perineal prostatectomy is not especially ill following the procedure, whereas the patient operated on by the suprapubic route is quite indisposed for a number of days thereafter. Laboratory findings also confirm this. Whereas with the suprapubic method the patient shows a high nonprotein nitrogen for a long time postoperatively, with the perineal method the nonprotein nitrogen is reduced to normal within from four to five days.

The lesser shock of the perineal prostatectomy makes it possible to perform a one-stage operation on patients who are quite weak and those who have disturbed kidney function. By the suprapubic method, such patients must be operated on in two stages often several weeks apart. This division of the operation into two stages has quite a distressing effect on the patient. The first stage of the procedure, the simple cystostomy, appears to him as major, and as dangerous an operation as the second stage in which the complete enucleation of the gland is performed. The necessity of undergoing two operative procedures frequently frightens the patient away from all operative intervention in his disease, or, as I have frequently experienced, drives him to a surgeon who will perform the perineal prostatectomy in one stage.

Perineal prostatectomy offers the additional advantage that the wound heals under more comfortable circumstances. The perineal wound is relatively painless and does not disturb the patient in any respect during respiration and expectoration. A suprapubic wound, under the best conditions, renders each cough and even each breath painful. The patient, therefore, usually breathes very superficially, and may retain detrimental secretions, which makes him more liable to post-

operative pulmonary complications than in perineal cases. Also, the perineal wound drains much better, which accounts for the fact that there are less wound complications or septic symptoms than in the suprapubic method. The immediate postoperative mortality is as small or perhaps even smaller. The perineal prostatectomy restores the anatomic relationships more normally than does the suprapubic method, for by sewing the urethral stump to the neck of the bladder, union between the bladder and the urethra is almost normally reconstructed. The latter fact may be proved later by a urethroscopic examination, when the colliculus seminalis may be seen, and the smooth transition from the urethra into the bladder observed. Also, by means of this perineal method in which the urethral stump is sewed to the bladder, the large pouch formed by the empty prostatic bed, which always remains after suprapubic method, is largely avoided, and the cause for postoperative formation of calculus and infection is prevented. Strictures of the neck of the bladder, which so frequently occur following suprapubic prostatectomy, are never experienced with this perineal method of prostatectomy.

Should it be discovered during the operation that the prostate is carcinomatous, it will be possible without any great extension of the wound to excise the carcinomatous tissue so thoroughly that in 30 per cent of these patients a permanent cure has been obtained. In this respect the perineal prostatectomy is vastly superior to the suprapubic method.

All of these undeniable advantages of perineal prostatectomy lead me, in spite of the improvements attained in recent years in the suprapubic method, to recommend perineal prostatectomy as the method of choice in prostatic hypertrophy. I use the suprapubic method only in those cases in which there is an unusual narrowness of the pelvic outlet, i. e., when the distance between the ischial tuberosities is less than two fingerbreadths, so that an insufficient view of the structures would be obtained by the perineal method, and in cases in which in addition to prostatic hypertrophy there is a bladder condition such as a diverticulum or tumor which alone would demand a suprapubic incision into the bladder.

The fear of postoperative disturbance of sexual potency should no longer prevent one from performing the perineal operation, even in younger patients. Increasing experience strengthens me in the impression that this particular technic of perineal prostatectomy does not disturb the sexual ability any more than does the suprapubic prostatectomy.

It has heretofore been frequently conceded by many surgeons that the reason they did not adopt perineal prostatectomy as a routine procedure was their aversion to its technical difficulties. This timidity



is really unjustified, as will quickly be recognized by those who will decide to perform the operation a number of times. They will quickly come to the conclusion that no great technical dexterity is necessary for its performance, merely a thorough knowledge of the anatomy of the perineum.

#### SUMMARY

1. The Wildbolz method in comparison with other perineal methods of prostatectomy is presented.

2. The method emphasizes the importance of both urethral sphincters and considers the urethral musculature as a single functional unit.

3. The incision in the prostatic capsule is placed as far as possible toward the bladder.

(a) It preserves the sphincters.

(b) Incontinence is eliminated.

(c) The nerves approaching the prostate gland are left mainly undisturbed.

(d) The patient's potency is usually not disturbed.

(e) Fistulas almost never occur.

4. Complete anatomic reconstruction of the prostatic region and urethra is carried out.

5. The operation is clearly visualized from beginning to end, thus:

(a) Exact hemostasis is possible.

(b) It is unlikely that a small piece of adenoma will be left behind.

6. The advantages of routine vasotomy to avoid epididymitis are discussed.

7. Postoperative treatment is outlined.

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# CIRCULAR SUTURE OF BLOOD VESSELS

## AN EXPERIMENTAL STUDY

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Obstruction of the lumen by blood clotting at the suture line is the chief hazard to the physiologic function of a blood vessel the ends of which have been joined by a circular suture. That this is the greatest risk in repair of a blood vessel is emphasized by many observers. Horsley,<sup>1</sup> Smith,<sup>2</sup> McNealy<sup>3</sup> and Buchanan<sup>4</sup> agreed that thromboses occur after many arterial sutures.

With the Carrel technic in skilled hands, according to Sofoteroff,<sup>5</sup> thrombosis occurs in a large percentage of cases. Moszkowicz<sup>6</sup> feared the circular suture because of thrombosis. A review<sup>7</sup> of the papers on vascular surgery written by important German surgeons and published during the World War reveals that the occurrence of early or progressive thrombosis after operations on arteries is frequent. It is a fair estimate in the opinion of that reviewer that in half of the cases in which a suture is made a viable artery is retained.

Before the World War, Matas<sup>8</sup> collected from the literature records of forty-nine circular sutures which had been performed in civilian

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hospitals and under conditions of peace. An analysis of the postoperative evidence revealed that 13.1 per cent had been followed by gangrene. Of the thirty-seven patients who recovered, in no less than thirty-three (87.6 per cent) the anastomosis had proved functionally valueless or superfluous if judged by the behavior of the peripheral pulses. In addition to the liability to occlusive thrombosis in the line of suture, which admittedly occurs in the absence of all infection, as a result solely of the trauma, Matas included the possibility of secondary hemorrhage from infection, panarteritis and the possibility of recurrence by yielding of the suture line as fallacies of direct arterial suture. In his opinion these failures are not overcome by the undoubted surgical successes of the German surgeons during the World War.

It cannot be questioned, in the opinion of La Roque,<sup>9</sup> that skilful suture is often followed by thrombosis, and he added that disappointment is apt to follow the expectation to secure information necessary to the solution of the problems from a study of clinical case reports in the literature. Carrel<sup>10</sup> found that failure is often due to the formation of a thrombus, but this is due to surgical causes,<sup>11</sup> and with the proper technic positive results can be secured.

Secondary hemorrhage as a sequel to arterial anastomoses is infrequent. In a study of twenty-nine instances of arterial suture reported in the literature, Buchanan<sup>4</sup> found no mention of hemorrhage. Aneurysm was not observed in this series, and Reid<sup>12</sup> noted that aneurysms do not develop in interposed venous grafts on arteries. Smith,<sup>2</sup> as well as Matas,<sup>8</sup> stated that aneurysm is a rare sequel to the suture of arteries. Stenosis of the sutured segment may occur from either the contraction of cicatricial tissue or from the organization of a thrombus. Cicatricial stenosis develops gradually. Bier<sup>13</sup> and most of the German surgeons frankly admit the uncertainty of the ultimate fate of the sutured vessel. They contend that even if the lumen at the suture line is ultimately obliterated, the gradual obstruction gives plenty of time for the establishment of ample collateral circulation.

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## EXPERIMENTAL STUDIES

In these studies experiments were made to secure information about the technical causes of failures to preserve the physiologic function of arteries joined by circular suture. Intermittently over a period of many months, arteries and veins of dogs were severed and the ends joined in various conditions of control. After the repair the results were studied within from a few hours to many months by examination post mortem or at reoperation.

*Series of Circular Sutures of Superficial Vessels.*—In seven strong, medium to large-sized dogs twenty-three end-to-end anastomoses of superficial arteries and veins were made. Each animal was given 1 grain (0.066 Gm.) of morphine sulphate subcutaneously, and anesthesia was produced by sodium iso-amylethylbarbiturate, given intravenously. Through wide exposure the vessels were brought up, the branches or tributaries ligated and the flow of blood interrupted by serrefines, the blades of which were covered by gauze. The vessels were cut by a sharp knife, and the tunica adventitia was removed. The intimal surfaces were cleansed of blood and kept moist by frequent washings with physiologic solution of sodium chloride in 100 cc. of which 1 dg. of heparin had been dissolved.

The solution of heparin used in all our experiments approximates the ideal for an anticoagulant. It has been used clinically in blood transfusions, and the evidence indicates that it may be employed with safety.<sup>14</sup> A water-soluble and thermostabile substance, heparin in solution retained its ability to prevent blood from clotting after four months. During this period it had been subjected on four occasions to 15 pounds (6.8 Kg.) of steam pressure for twenty minutes in the autoclave. Heparin was isolated by Howell,<sup>15</sup> and was described as an antiprothrombin which prevents the calcium of the plasma from activating prothrombin into thrombin.<sup>16</sup> Howell considered that the effect of the thromboplastic substances of injured tissues and of injured blood platelets is to neutralize the antiprothrombin or heparin of the blood. Muscle tissue, when injured, the liver, the lungs and the kidneys are rich in thromboplastic substances. The walls of the blood vessels are especially rich in these "coagulins."<sup>17</sup> Wells<sup>16</sup> recalled that the joint action of the tissues and blood thromboplastic substances is greater than the sum of their individual actions. The heparin solution neutralizes the

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14. Reed, C. J.: Practical Uses of Heparin, J. Lab. & Clin. Med. **14**:243, 1928.

15. Howell, W. H.: Purification of Heparin and Its Chemical and Physiological Reactions, Bull. Johns Hopkins Hosp. **42**:199, 1928.

16. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 350.

17. Loeb, Leo: Univ. Pennsylvania M. Bull. **16**:382, 1904; cited by Wells.<sup>16</sup>

thromboplastic substances coming from the injured wall of the blood vessel. Its disadvantage is that it may not be available in emergency vascular repair.

The Carrel triangular suture technic was used, with the finest silk and human hair in number 16 straight needles sterilized and kept in liquid petrolatum. Care was used to keep each line on a tension while suturing to prevent narrowing at the suture line. The serrefines were removed promptly when the suture was completed. No secondary sutures

TABLE 1.—*Series of Circular Sutures of Superficial Vessels\**

Animal Number	Vessels Joined by Anastomosis	Date of Operation	Date of Examination	Time, Days	Findings
4	Suture of left common carotid.....	8/10/30	†		
7	Proximal right to distal left carotid..	7/31/30	8/15/30	15	No thrombosis or stenosis
7	Previous anastomosis resected; ends rejoined	8/15/30	11/ 2/30	79	No thrombosis or stenosis
7‡	Anastomosis resected; ends rejoined..	11/ 2/30	1/31/31	90	No thrombosis or stenosis
8	Right femoral cut; ends rejoined.....	8/17/30	10/ 5/30	49	Complete stenosis
8	Proximal right carotid to distal left external jugular vein	8/17/30	10/ 5/30	49	Complete stenosis
8§	Proximal left carotid to distal right carotid	8/17/30	10/ 5/30	49	Complete stenosis
9	Suture of right common carotid.....	8/15/30	9/ 7/30	23	No thrombosis or stenosis
9‡	Anastomosis resected; ends rejoined..	9/ 7/30	12/29/30	113	Complete stenosis
10	Suture of right common carotid.....	8/10/30	9/ 7/30	28	No thrombosis or stenosis
10	Suture of right external jugular vein	8/10/30	9/ 7/30	28	No thrombosis or stenosis
10	Suture of left external jugular vein..	9/ 7/30	11/ 2/30	56	No thrombosis or stenosis
10	Anastomosis right external jugular vein resected; resutured	9/ 7/30	11/ 2/30	56	No thrombosis or stenosis
10	Cross-anastomosis of carotids.....	9/ 7/30	11/ 2/30	56	No thrombosis or stenosis
10	Resection of cross-anastomosis; ends rejoined	11/ 2/30	:	..	No further examination
11	Proximal right carotid to proximal left external jugular vein	8/17/30	11/ 2/30	77	Complete stenosis
11	Proximal left carotid to distal right carotid	8/17/30	11/ 2/30	77	Complete stenosis
11	Carotid suture removed; ends rejoined	11/ 2/30	1/31/31	90	Complete stenosis
12	Jugular vein transplanted to right carotid	10/ 5/30	11/ 2/30	28	Complete stenosis
12	Left carotid cut; ends rejoined.....	10/ 5/30	11/ 2/30	28	Complete stenosis
12‡	Right iliac vein transplanted to right iliac artery	10/ 5/30	11/ 2/30	28	Complete stenosis

\* Sodium iso-amylethylbarbiturate anesthesia was used intravenously throughout. Stenosis was observed in 52.6 per cent of the circular sutures of this series.

† This animal was lost. No further examination was made.

‡ Ordered killed because of epidemic of rabies. No further examination made.

§ This animal died on Oct. 20, 1930. For two days preceding death there was spastic paralysis. On broad surfaces made by sectioning the hardened brain, there were no gross areas of focal necrosis.

were made. After several minutes' observation to see that no thrombosis occurred, the sheath of the vessel was closed, and when convenient, viable muscle was tucked snugly about the vessel.

Examinations of these vessels were made from fifteen to one hundred and thirteen days after operation. Complete stenosis was observed in 52.6 per cent of the vessels examined (table 1). Stenosis in these instances may have followed thrombosis. That this occurred in animal

8 is improbable. Both common carotid arteries supplying the brain were stenosed after forty-nine days. Necrosis of the brain would have followed sudden obstruction by clotting. This did not occur, however, for the animal lived normally until after the segments were removed. On broad surfaces made by sectioning the hardened brain removed at autopsy, no areas of necrosis were seen. In four other instances, for from 2 to 5 cm. on either side of the stenosed suture line, there was freshly clotted blood in the lumen, indicating that complete occlusion had preceded the examination by only a short time.

While proof is lacking, we conclude from our observations that stenosis in these small vessels is often due to the contraction of the dense fibrous capsule or callus that forms outside the vessel at the suture line and extends from 5 to 10 mm. in either direction along its wall. This is not of practical interest, for in clinical surgery vessels of this size would never be sutured.

*Series of Circular Sutures of Deep Vessels.*—(A) End-to-End Anastomoses of the Aorta: The abdominal part of the aorta in medium to large-sized dogs is more nearly the size of vessels usually sutured in man. With the blood circulating through them, their maximum diameter varies from 8 to 11 mm. In fifty-one animals the aorta was exposed through a longitudinal ventral incision, its branches were ligated for 2 cm., and the flow of blood was interrupted by two strips of tape 5 mm. wide passed completely around it, the ends of the tape being held by small pile clamps. In fifty animals the aorta was severed, and the ends were rejoined. In one (animal 27), the central end of the aorta was united to the distal end of the inferior vena cava (table 2).

The aorta was cut by a sharp knife 1 cm. proximal to the origin of the inferior mesenteric artery. The ends of the tunica adventitia were grasped by Graefe plain fixation forceps and as much removed as could be pulled past the ends of the vessel. The blood was carefully washed out, and the intimal surfaces were kept moist with heparin solution. Except as mentioned, all oozing of blood was stopped before proceeding with the suture. In two instances, the Bier-Moure two-point suspension technic<sup>13</sup> was used; in all others, the Carrel prismatic suture was employed. Number 00 chromicized catgut on a curved swedged needle was used for ten sutures; for the remainder, black waxed A silk on Carrel curved blood vessel needles. Prepared in phenolized beeswax after the manner devised by Moses Gunn and described by McArthur,<sup>18</sup> the silk is smooth and solid like silkworm gut, is stronger than before waxing and is much more easily handled in deep wounds.

18. McArthur, I. L.: Preparation of Waxed Silk, Surg., Gynec. & Obst. **16**: 460, 1913.

In our work we made this departure from the original Carrel technic: To form the posterior point of the triangle we placed two traction sutures through the edges of the vessel and closely together in the back wall. The ends of one were brought out to the right, the ends of the other, to the left, of the vessel. Time is saved when working in a deep wound by not having to pass the traction suture behind the vessel. Moreover, the artery need not be freed from its collateral vessels for so great a distance. Thus, the collateral circulation is better preserved. The importance of this is stressed by Bier, Matas<sup>19</sup> and Makins, for if gradual thrombosis or stenosis should occur, the uninjured collaterals might assume the function of the obstructed vessel.

The ends of the artery are apposed by tying the retaining stitches. An end of one of the posterior retention sutures is threaded into the needle, and a side of the triangle is sutured. Instead of tying the stitch to the traction thread at each corner as suggested by Bernheim,<sup>19</sup> we discovered that a lock stitch is much better. The last stitch of the line, taken 1 mm. from the traction suture, is the lock stitch. This prevents the line of suture from loosening or from being drawn too taut by subsequent pulling. When the second posterior traction suture is reached, the continuous suture is tied to one of its ends. The suture line is then carefully inspected; accessory sutures are taken if needed, and the flow of blood is reestablished. The distal tape is removed first, and the proximal as quickly as possible. Bleeding will occur, but a sponge pressed tightly will control it. A thin strip of muscle held closely to the suture line, as suggested by Bird,<sup>20</sup> hastens clotting in the needle holes. When the bleeding stops, the ends of the tunica adventitia are brought over the suture line by interrupted stitches, the vessel sheath closed and the edges of the peritoneum apposed.

In this study we are interested chiefly in thrombosis complicating the circular suture of the blood vessels. Before proceeding further, some of the etiologic factors of thrombosis will be considered. Aschoff<sup>21</sup> reminded us that there is not a single cause but a number of different conditions which are closely interrelated in the occurrence of thrombosis:

1. The factor of trauma. Traumatic injury to the intima is an important element, but McLean<sup>22</sup> has shown that endothelial damage per se is not a cause of thrombosis. He crushed the veins of dogs and repeated the procedure in forty-eight hours, yet was unable to produce

19. Bernheim, B. M.: *Surgery of the Vascular System*, Philadelphia, J. B. Lippincott Company, 1913.

20. Bird, C. E.: *Anastomosis of Veins*, Surg., Gynec. & Obst. **42**:428, 1926.

21. Aschoff, L.: *Lectures on Pathology*, New York, Paul B. Hoeber, Inc., 1924.

22. McLean, Angus: *Thrombosis and Embolism*, Surg., Gynec. & Obst. **20**: 457, 1915.



thrombosis at the site of repeated crushing. Murphy<sup>23</sup> observed that arteries penetrated by bullets rarely become occluded by blood clots.

2. The element of stasis and slowing of the blood stream. Stasis of the blood stream of itself does not produce thrombosis. This has been shown by the famous living test tube experiments of Hunter and Durante,<sup>24</sup> Glenard and others. Blood in a segment of artery or vein between two sterile ligatures remains fluid for hours, days and weeks. Welch, in his classic monograph on thrombosis,<sup>25</sup> expressed the opinion that slowing of the blood stream is not a sufficient cause, but is important when combined with other factors such as trauma and infection. In certain experiments in extracorporeal thrombus formation performed on rabbits, Rowntree and Shionoya<sup>26</sup> found that the conditions tending to retard the circulation hastened the progress of clotting. Conversely, when circulatory stimuli such as thyroxine and ephedrine were injected into the animals, the circulation was maintained longer than normal.

3. The factor of infection. Infection may play a rôle in thrombosis. The experiments of McLean<sup>22</sup> are instructive. After crushing the wall of a vein he introduced a twenty-four hour bouillon culture of *Staphylococcus aureus* into the vein and again crushed it to work the organisms into its walls. No thrombi were found at the site of the injury. Sterile threads were suspended in the veins, and no clots formed on them. When threads infected by soaking in cultures of bacteria were suspended in the veins, clots formed and occluded their lumens.

4. Changes within the blood. Lee and Vincent,<sup>27</sup> by experiments, showed that the coagulation time depends on the number of blood platelets present. Welch<sup>25</sup> observed that the platelets are increased in chlorosis of which thrombosis is a well recognized complication. Hueck<sup>24</sup> noted a marked increase in the platelet count up to about the thirteenth day after operation, depending on its severity. Dawbarn and his associates<sup>28</sup> obtained similar results. They found that the number of plate-

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23. Murphy, J. B.: Resection of Arteries and Veins Injured in Continuity: End to End Suture, *M. Rec.* **51**:73, 1897.

24. Cited by Hosoi, K.: Postoperative Thrombosis, Pulmonary Embolism and Infarction, *Internat. S. Digest* **13**:67, 1932.

25. Welch, W. H.: Thrombosis, in Albutt, T. C., and Rolleston, H. D.: *A System of Medicine*, New York, The Macmillan Company, 1899, vol. 7, p. 153.

26. Rowntree, L. G., and Shionoya, T.: Studies in Experimental Extracorporeal Thrombosis, *J. Exper. Med.* **46**:7, 1927.

27. Lee, R. I., and Vincent, B.: The Coagulation of Normal Human Blood: An Experimental Study, *Arch. Int. Med.* **13**:398 (March) 1914.

28. Dawbarn, R. Y.; Earlam, F., and Evans, W. H.: Relation of the Blood Platelets to Thrombosis After Operation and Parturition, *J. Path. & Bact.* **31**:833, 1928.

lets begins to rise on the sixth day, reaches a maximum about the tenth day after operation and persists for a further four or five days, normal figures being reached in about three weeks. Gage,<sup>24</sup> who reviewed the literature on blood platelets, concluded that the platelet count in the circulating blood reaches its highest about the time of the appearance of clinical thrombosis. Tissue fibrinogen, given subcutaneously or by mouth, also alters the blood so as to shorten the clotting time.<sup>29</sup>

In all of these experiments the element of injury was present. In thirty-three, sodium iso-amylethylbarbiturate was given intravenously for anesthesia. When used intravenously in clinical surgery, observers<sup>30</sup> find a reduction in the blood pressure. In one series,<sup>31</sup> the systolic pressure was reduced an average of 46 mm. of mercury; the diastolic, 23 mm. No measure of the blood pressure in these animals was made, but a profound anesthesia was maintained, in many, until death of the animal occurred. Nineteen were killed and examined within forty-eight hours. In ten of these thrombosis was found; in eight, the thrombus obstructed the lumen. Early in our studies we found that thrombosis could be predicted definitely because of slight oozing of blood from a collateral not properly ligated. We have denoted these as anticipated thrombi. Six of the occlusive thrombi were anticipated, leaving two instances of unexplained occlusive thrombi occurring with this anesthetic. Ether anesthesia was used eighteen times. Thrombi were found four times; an obliterating clot was found once, and its occurrence was predicted. Of this series of fifty-one animals, five were not examined because of extensive postmortem changes.

In sixteen animals from 2 to 6 cc. of fibrogen, a purified tissue fibrinogen, prepared and furnished by the William S. Merrell Company, was given intramuscularly one hour before operation. No determinations of the clotting time were made. In each instance a quick clotting reaction of the blood was noted. This tissue fibrinogen was used in seven animals having sodium iso-amylethylbarbiturate anesthesia and in nine having ether anesthesia. One of the sixteen animals was not examined. Occlusive thrombosis occurred once with each anesthetic, and in both the clotting was anticipated.

Infection was the cause of death in seven animals. In two of these it was induced. For one (animal 71), from a twenty-four hour bouillon culture of *Staphylococcus aureus*, sufficient was taken to fill the segment

29. Mills, C. A.: Do Blood Platelets, Plasma and Tissues Yield Thrombin, or Tissue Fibrinogen? *Am. J. Physiol.* **95**:1, 1930; Considerations of the Problem of Blood Clotting, *Am. J. M. Sc.* **172**:501, 1926.

30. Sise, L. F.: Intravenous Sodium Isoamylethyl Barbiturate with Spinal Anesthesia, *Am. J. Surg.* **9**:65, 1930.

31. Ranson, B. B., Jr., and McLellan, G. A.: Induction Anesthesia by Sodium Amytal, *Am. J. Surg.* **9**:60, 1930.

of aorta and to bathe the suture line during the suturing. The toxins of *Staphylococcus aureus* produce clotting more readily than those of other organisms examined by Loeb,<sup>32</sup> while those of *Bacillus coli* have an intermediary place. In another animal (number 73), a small gauze sponge infected with floor dirt was placed outside the suture line next to the aorta. A violent peritonitis occurred in five others. At autopsy, from two to thirteen days after operation, no endovasal thrombi were found in any of the animals. Four of these animals had received sodium iso-amylethylbarbiturate anesthesia.

Of the twenty-four animals having sutures of the deep vessels, including the venous transplants, examined or living after one month, in only one (number 13) was an aneurysm observed (4.1 per cent) and in another (number 10), stenosis (4.1 per cent). Chromicized catgut was the suture, and, when absorbed, the suture line relaxed, producing a small saccular aneurysm 8 mm. in diameter. In clinical surgery one would not use chromicized catgut. When the eleven sutured with chromicized catgut were examined, obstructing thrombi were found in two. Each of these was anticipated because of blood oozing from the ends of the aorta.

Stenosis (number 10) was produced by the organization of a slowly forming obliterative thrombus. The protocol for this animal follows.

ANIMAL 10.—On June 20, 1931, the aorta was cut, and the ends were joined by number 00 chromicized catgut. There was a good femoral pulse on the following day. On June 29, the animal was active, but the femoral pulses were weak. On July 3 and 23, no femoral pulse could be felt. On May 7, 1932, there were strong femoral pulses. The abdomen was opened and the aorta exposed. A segment of the aorta 4 cm. long was removed, 2 cm. of which was a fibrous cord. There was a good collateral circulation. A piece of the right external jugular vein was transplanted to fill the gap.

(B) Transplantation of Venous Segments to the Aorta: Segments of veins were grafted to the abdominal aorta in twenty-nine dogs. In six the site of a previous anastomosis was removed. But for one ether anesthesia was used throughout. The tissue fibrinogen, fibrogen, was given to five. The triangular suture of black waxed A silk was used. Great care was taken to evert the edges of the veins. To best secure eversion, we placed the retaining stitches as "mattress-on-edge" sutures. The tissue "coagulins" were neutralized and the intimal surfaces cleansed and moistened by the solution of heparin. Intravascular clotting is more favored by conditions found in venous grafting. On examination post mortem, thrombi were found in fourteen of the twenty-seven animals; two of the animals are living. In five segments the lumen was completely obstructed. Three of the five clots were anticipated (table 2).

32. Loeb, Leo: The Influence of Certain Bacteria on the Coagulation of Blood, J. M. Research 10:407, 1903.

TABLE 2.—*Series of Circular Sutures of Deep Vessels*

Animal Number	Group A: End-to-End Anastomoses of the Aorta (51 Dogs)																				
	Ether	Sodium Iso-Amlyl-ethylbarbiturate	Fibrogen	Thrombosis		Time Interval Between Operation and Examination										Absorbable Suture	Aneurysm	Stenosis	Hemorrhage	No Examination	Living
				Of Any Degree	Occlusive	Anticipated	Less Than 24 Hours	24 Hours	48 Hours	72 Hours	1 Days to 1 Month	1 to 6 Months	6 Months or More	Infection							
1	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
2	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
3	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
4	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
5	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
6	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
7	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
8	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
9	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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11	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
12	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
13	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
14	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
15	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
16	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
17	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
18	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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20	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
21	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
22	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
23	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
24	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
25	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
26	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
27	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
28	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
29	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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31	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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34	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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36	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
37	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
38	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
39	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
40	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
41	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
42	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
43	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
44	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
45	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
46	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
47	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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49	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
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51	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
52	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
53	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
54	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
55	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
56	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
57	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
58	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
59	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
60	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
61	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
62	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
63	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
64	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
65	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
66	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
67	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
68	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
69	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
70	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
71	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
72	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			
73	:	+	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:			

Group B: Transplantation of Venous Segments to Aorta (29 Dogs)

[illegible]

*Eddying Currents of von Recklinghausen.*—This was observed in the following experiment.

ANIMAL 61.—On Dec. 5, 1931, the abdominal part of the aorta was severed, 1 cm. was removed, and 1.5 cm. of the inferior vena cava was grafted into the gap. The animal died from peritonitis on December 9. At autopsy, the suture lines of the vessels were intact. Molded to the shape and size of the graft and tightly attached to each line of suture was a firm cylindric clot with a lumen 5 mm. in diameter.

Another instance parallel to this was found (animal 4). Although not in itself sufficient to cause thrombosis, von Recklinghausen<sup>33</sup> attached more importance to the whirling or eddying motion than to mere slowness of the circulation. Eddies are produced when blood enters normal or pathologic, dilated channels from small ones. The external jugular vein has a diameter about equal to that of the aorta. No cylindric thrombi were found within those pieces (in all, twenty-three) of external jugular vein grafted to the aorta. To avoid the eddying currents, a vein smaller than that accompanying the injured artery should be used for grafts.

*The Deliberate Removal of Obstructing Tapes.*—This was carried out on the following animal:

ANIMAL 10.—On May 27, 1932, the obstructed fibrous segment of the aorta, sutured with number 00 chromicized catgut on June 20, 1931, was removed, and a piece of the right external jugular vein was transplanted to its place. When the suturing was completed, the distal obstructing tape was released. Oozing from the suture line occurred for sixty seconds before the proximal tape was removed. The femoral pulse was weak when the abdomen was closed. At postmortem examination twenty-four hours later, there was a firm clot completely filling the segment of vein. This is illustrative of similar other observations.

Following a venous graft on the aorta, the lines of the completed suture are carefully inspected and complementary stitches taken if needed. An immediate release of the full pulsating current is made. According to Howell's hypothesis, clotting does not occur when the flow is rapid, for ample antiprothrombin is carried to neutralize the "coagulins" where liberated. Eberth and Schimmelbusch<sup>34</sup> found that under normal conditions the platelets circulate with red corpuscles in the axial blood current, but make their appearance in the outer still zone, which is from eight to twenty times slower when the rapidity of the circulation is sufficiently diminished. Each thrombus starts as a white thrombus, and its building stones are the blood platelets. The adhesive surfaces of the intima injured at the suture line inflict dam-

33. von Recklinghausen: *Handbuch der allgemeinen Pathologie des Kreislaufs und der Ernährung*. Stuttgart, 1893; cited by Welch.<sup>25</sup>

34. Eberth, C. J., and Schimmelbusch, C.: *Die Thrombose nach Versuchen und Leichenbefunden*. Stuttgart, Ferdinand Enke, 1888; cited by Welch.<sup>25</sup>

ages on the platelets. The forceful pulsating current in the artery prevents adhesions of the platelets or the accumulation of formed elements at the site of injury. Hence, every effort should be made to restore the forceful current before the nidus of a clot is formed by stagnant blood. Welch<sup>24</sup> noted that a clot itself is a foreign body and may lead to a further extension of a thrombus. Thrombi seem to have certain self-propagating powers.

*Effects of the Valves.*—Valves in two of the grafts on the aorta were responsible for clots partly obstructing the flow of blood. In one, placed so as to retard the current, a clot was attached to the proximal suture line, half filled the lumen and extended to a cusp of the valve. In the other, turned so that the blood current kept the valves open, mural thrombi formed behind each cusp. Grafted segments should be implanted so that their valves are kept open by the current of blood; that is to say, the central end in the venous system should become the distal end in the arterial circuit.

*Injury to the Intima.*—Shaggy, scalelike mural thrombi, from 5 to 7 mm. in diameter, were found in three grafts. None was obstructive. About one-fourth the intima in one piece of vein was covered by these flat plaques of blood clot. Gentleness in handling the vein is imperative. Forceful sponging during its exposure is to be avoided. The intima is kept moist at all times. The influence of the smooth non-adhesive endothelium is of first importance in maintaining fluidity of the blood. Endothelial cells altered by injury may act as foreign substances and induce small mural thrombi to form.

*Infection.*—The following experiment was carried out:

ANIMAL 30.—On May 4, 1932, under ether anesthesia, 2 cm. of the right external jugular vein was grafted on the aorta. One end of a thread dipped in a twenty-four hour bouillon culture of *Bacillus coli* was suspended in the vein. The abdomen was closed, and in twenty-four hours the animal was killed. A pear-shaped clot with the thread in its center filled the vessel. There was no attachment to either line of anastomosis.

This experiment confirms the findings of McLean.<sup>22</sup>

In another animal (number 55), after completing the suture, fluid from a twenty-four hour broth culture of *Bacillus coli* was held in the repaired vessel for two minutes. After forty-eight hours, the animal was killed. There were no clots.

#### COMMENT

Of the causes generally recognized in the etiology of thrombosis, trauma is a constant factor in repair of the vessels. Alteration in the rate of flow of the blood current plays a more important rôle than is usually considered. Occlusive thrombosis can be predicted with great

accuracy when blood sluggishly oozes from the terminals of the vessel. Heparin solution, unless applied constantly, is powerless to prevent it. Similarly, blood sluggishly flowing from a gradual release of the circulation will in a few seconds congeal enough to vitiate the repair. There is a natural reluctance of the operating surgeon to establishing the full flow of blood until he sees what happens at the line of suture. This reluctance should be overcome. Watson and Makins<sup>35</sup> suggested placing a rubber drainage tube between the tape and the artery to protect the artery from injury by the tape. This has another commendable feature. The rubber tube serves as a guide for the scissors so that the tape can be cut quickly, at once releasing the full flow of blood. A rapid return of the pulsating current prevents damage to the formed elements and dilutes or neutralizes the thromboplastic substances of the tissues. Grafts should be the diameter of the repaired artery and constricted suture lines avoided in order to prevent eddying currents.

In our studies it does not appear that clotting is appreciably influenced by any changes in the rate of flow resulting from profound anesthesia with sodium iso-amylethylbarbiturate. It is our opinion that the nidus of most thrombi forms in the short interval between the time blood enters and the time of the establishment of the free forceful flow through the repaired vessel. Gradual obliterative thrombosis probably results from the self-propagation of this original nidus.

The rôle accorded infection in thrombosis complicating vascular surgery has been overemphasized. No clotting occurred even when the vessels were inoculated with pure cultures. Infections in other parts of the body, viz., a virulent peritonitis and infections of the areolar tissues of the abdominal wall, produced no intravascular clots. The strictest asepsis should be practiced, for an infected suture line leads to necrosis and hemorrhage, which are more serious than thrombosis. That suture should be attempted in the presence of infection of a wound is questionable, but instances are reported by German surgeons with a successful outcome.

There is no evidence from our studies that changes within the blood enhanced clotting in the least. Efforts were not made to measure the changes in the numbers of platelets after operation. According to the observations of Dawbarn and his associates,<sup>28</sup> there was increase in the platelets on the sixth day. Assuming that the platelet count rose in the same way in the animals of our series, this had no influence on the clotting. Obstructive thrombosis did not occur in thirty-five of thirty-seven animals that lived seventy-two hours or longer (two remain alive). While tissue fibrinogen (table 3), given to a small number, noticeably quickened clotting, it did not influence the intravascular clotting.

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35. Watson and Makins, cited by Matas.<sup>8</sup>

Segments removed from animals 29, 30 and 55, seven and one-half, seven and one-half and six months, respectively, after operation, were hardened and sectioned. Sections stained according to Weigert's method were studied. There is no evidence that the elastic elements of the tunica media are being substituted for the fibrous scar tissue. Likewise, Neff<sup>36</sup> and Reid<sup>12</sup> found that there is only a fibrous union.

Carrel<sup>11</sup> observed that the vein transplanted on an artery reacts against the increase of blood pressure by thickening of its walls. Veins follow the law of adaptation of an organ to function and can fill the

TABLE 3.—Data Pertaining to Use of Fibrogen \*

Group A: End-to-End Circular Sutures of the Aorta (16 Instances)						
Animal Number	Ether	Sodium Iso-Amylethyl-barbiturate	Thrombosis	Thrombosis Predicted	Occlusive Thrombosis	No Autopsy
27	..	+	+	+	+	..
28	..	+	..	..	..	..
29	..	+	..	..	..	..
30	..	+	..	..	..	..
32	..	—	..	..	..	..
33	..	+	..	..	..	..
34	..	+	..	..	..	..
39	—	..	..	..	..	..
43	+	..	..	..	..	..
44	+	..	..	..	..	..
45	+	..	..	..	..	..
47	+	..	+	..	..	..
48	+	..	..	..	..	..
50	—	..	+	+	+	..
54	+	..	..	..	..	+
55	—	..	..	..	..	+
Group B: Transplantation of Venous Segments into Aorta (5 Instances)						
10	+	..	+	—	—	..
29	+	..	..	—	—	..
30	+	..	+	—	—	..
53	+	..	—	..	..	..
55	+	..	..	..	..	..

\* Used intramuscularly in amounts of from 2 to 6 cc.; no increase in thrombi formation resulted from the use of fibrogen. The use of fibrogen combined with sodium iso-amylethyl-barbiturate anesthesia caused no increase in thrombi formation.

rôle of arteries when necessary. Matas<sup>37</sup> noted that veins have great tolerance for trauma, while Reid<sup>12</sup> stated that veins adapt themselves much more readily to mechanical disturbances than do arteries. Examined after from four to eight weeks, there was no stretching of the wall of the veins implanted on the arteries in animals 64, 68 and 72. Moreover, their walls were thick, with fibrous tissue proliferation from the sheath of the vessel. Veins subjected to the increased blood pressure that is usual in arteries should be observed for from eight to ten years. The surgical literature contains no record of such observations. Placed in their natural habitat on the farm, animals 70 and 76 will be observed, it is hoped, for a few years.

36. Neff, J. M.: Blood Vessel Suture, Surg., Gynec. & Obst. **33**:657, 1921.

37. Matas, Rudolph: The Suture in the Surgery of the Vascular System, Tr. M. A. Alabama, 1905, p. 245.



## CONCLUSIONS

1. Surgical trauma and retardation or distortion of the blood current are the chief contributing factors to the thrombosis that occurs where blood vessels are sutured.

2. Infection plays a minor rôle as a cause of blood clotting at the suture line. Careful asepsis is essential to preclude breaking down of the suture line.

3. An obstructing thrombus, when it occurs, usually forms within a few hours after vascular repair. It is secondary usually to platelets deposited before the full flow of blood is released.

4. The increase in blood platelets does not reach its maximum until a few days after operation, usually too late to influence thrombosis in the segment of repair.

5. Heparin solution fulfils the requirements of a satisfactory anti-coagulant in suture of the blood vessels.

6. A method of suturing is described which requires the ligation of a minimum of the collateral circulation.

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# STAINING OF CARTILAGE

## GROSS STAINING BY INTRA-ARTICULAR INJECTION OF DYES IN ANIMALS

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We have been able to find only two articles on the gross staining of cartilage in addition to those already reviewed.<sup>1</sup> A modification of the Lundwall method by Moreira da Rocha<sup>2</sup> referred to the staining of cartilage by methylene blue (methylthionine chloride, U. S. P.), toluidine blue, methyl violet, methyl green and safranin. Staining of joint cartilage was referred to only by implication; staining in the closed joint was not discussed. The author concluded that "no matter the stain used, its electivity for staining and its stability are in direct ratio not only to the maturity of amorphous ground substance of cartilage but also to its quantity." Thus it is found that adult hyaline cartilage will stain better and more strongly than embryonal cartilage of any type or adult cartilage of elastic or fibrous type. Da Rocha stated that this method of studying cartilage is better than desiccation or maceration. This study is, of course, of fundamental collateral interest. Crowe<sup>3</sup> injected isamine blue intravenously, and on killing the animal (rabbit) two days later noted a selective staining of diseased areas in the cartilage in streptococcic arthritis (experimentally produced). Marrow was also stained. In the specimens shown us by Dr. Crowe, there were definite staining of marrow and uniform staining of joint cartilage, but no definitely diseased areas in cartilage were seen. The stained cartilage was a light, clear blue.

### METHOD

In this study we have further noted the action of dyes on joint cartilage, with special reference to selectivity of staining of diseased areas in cartilage. In general our experimental course has been this:

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From the Laboratory Division, Hospital for Joint Diseases.

1. Burman, M. S.: The Selective Staining of Diseased Areas in Cartilage by the Intra-Articular Injection of Dyes, with Special Reference to Arthroscopy: An Experimental Cadaver Study, *Arch. Surg.* **26**:153 (Jan.) 1933.

2. Moreira da Rocha, J.: Staining of Adult Cartilage by Lundwall's Method. *Anat. Rec.* **13**:447, 1917.

3. Crowe, H. W.: Streptococcal Lesions in Rabbit Demonstrated by Intra-Vital Staining, *Tr. M. Soc., London* **53**:94, 1930; personal communication.

In one group of animals (rabbits and guinea-pigs), the dye chosen was injected into the knee joint under amytal anesthesia (70 mg. per kilogram of body weight injected intraperitoneally). Occasionally it was necessary to support the amytal with ether. The joints into which injections had been made were examined either immediately or from two to nine days later, to determine the fate of the dye and the gross reaction of the joint to the dye. In most cases, the abdomen was opened and the retroperitoneal region exposed to the action of filtered ultraviolet radiation (Wood's light) to see if there was any absorption of the dye by the lumbar lymph nodes.<sup>4</sup> In no case were we able to demonstrate dye in the glands. In a second group of animals (rabbits only), the cartilage was traumatized by injuring the cartilage and synovia of the knee joint by the insertion of a large bore needle into the closed joint. It is not difficult to localize the point of the needle, and one can easily feel what structures are being injured. It is necessary to use force to create a defect in cartilage, always a bit more force than one thinks is required. This method is simpler than, and as sure as, the more time-consuming method of open operation (Key<sup>5</sup>). At a varying interval after the operation, injections of the dye chosen were made into the knee joint. The joint was then opened at once.

*Choice of Dyes.*—It is obvious that the use of alcoholic dye solutions intra-articularly is contraindicated; hence all the dyes used were dissolved in water. The relation between the  $p_H$  of the dye and that of the joint fluid and the resultant staining was not studied. In fact, it is very difficult to obtain even a drop of synovial fluid from these small joints for examination. The joint is simply moist, and there is no accumulation of fluid. The amount of dye injected was usually not more than 2 cc., 0.5 or 1 cc. often being enough to distend the joint. One should make the injection with the needle in the quadriceps bursa, the needle being held parallel to the bursa. It is sometimes difficult to enter the joint, but easy flow and withdrawal of dye indicate that the joint is being distended. The distention of the quadriceps bursa may at times also be felt. Occasionally a little of the dye will appear subcutaneously, owing possibly to the sharp bevel of the needle. One should guard against fascial and intermuscular injection of the dye.

Both acid and basic dyes were used. Dyes were selected from the most important groups of dyes, the chromophore grouping, which is here outlined (after Conn<sup>6</sup>), being used.

#### *Dyes Grouped by Chromophores*

1. Nitro dyes
2. Azo dyes
3. Oxyquinone dyes
4. Quinone imide dyes
  - (a) indamins
  - (b) thiazins
  - (c) oxazins
  - (d) azins, which include
    - (1) amido-azins
    - (2) safranins
    - (3) indulins

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4. Rynearson, E. H.: The Macrophage in Absorption from the Synovial Cavity, *J. Bone & Joint Surg.* **13**:127, 1931. Kuhns, J.: Lymphatic Drainage of Knee and Ankle Joints, *J. Bone & Joint Surg.* **11**:412, 1929.

5. Key, J. A.: Experimental Arthritis: The Changes in Joints Produced by Creating Defects in the Articular Cartilage, *J. Bone & Joint Surg.* **13**:725, 1931.

6. Conn, H. J.: *Biological Stains: A Handbook on the Nature and Uses of the Dyes Employed in the Biological Laboratory*, ed. 2, Geneva, N. Y., Commission on Standardization of Biologic Stains, 1929.

5. Phenylmethane dyes
  - (a) di-phenylmethanes
  - (b) di-amino-tri-phenylmethanes
  - (c) tri-amino-tri-phenylmethanes
  - (d) hydroxy-tri-phenylmethanes
6. Xanthine dyes, including
  - (a) pyronins
  - (b) rhodamines
  - (c) fluorane derivatives
  - (d) phenolphthaleins and sulphophthaleins

Trypan blue is an acid azo dye. Of the oxyquinone group, alizarin, which is almost insoluble in water, was used, purpurin not being available. Of the thiazin subgroup of the larger quinone imide group, methylene blue was used. Toluidine blue was not employed in this series of experiments, having previously been noted as a dye which stains cartilage uniformly. Of the amido-azin subgroup, neutral red was used; it had previously been indicated as a possible selective dye. Of the safranins, safranin O was used. Janus green is an azo dye, as well as an azin, and is related to safranin. Gentian violet and aniline blue represented the tri-amino-tri-phenyl methanes. Isamine blue (also called pyrrhol blue, Ehrlich) is a sulphonated tri-beta-naphthyl-pararosanilin, and hence belongs in this group. The fluoranes were represented by eosin and mercurochrome. Alum carmine, a cochineal derivative, was the only natural dye used. Lithium carmine was not used.

The nitro dyes, as picric acid, were not tested. Of the azo dyes, Bismarck brown and sudan III had previously been used and shown to be quite ineffectual in staining cartilage. The other dye groups were not used, because the dyes within the groups were not available. The phenolphthaleins and sulphophthaleins are indicators and hence were not used. The effect of litmus was noted previously.

## RESULTS

*Effect of Dyes on Normal Joints.*—Six knee joints of three guinea-pigs were studied. A 1 per cent solution of isamine blue was injected into two knees; one was examined at once, and one three days later. A 0.5 per cent solution of gentian violet was injected into one knee; the joint was examined at once. A 1 per cent solution of mercurochrome was used in three knees; in one case, the knee was examined at once; in the other cases, one and two days after injection, respectively.

The stains dyed cartilage uniformly and superficially over a wide area. The stains were not washed away on rinsing. All other structures in the joint, such as synovia and menisci, were also stained, though possibly less uniformly. Some of the intra-articular structures, such as the crucial ligaments, stained with difficulty. Three of the joints were examined immediately after injection, and three from two to three days later. The intensity of staining had become less, and the uniformity of staining more patchy, which indicated either absorption of the dye or wearing away by movement of the joint. No reaction to these dyes was noted, either in cartilage or in synovia; no exudate was present. In two cases, the dye did not enter the joint cavity proper

but was in the muscle and fascia. It should be noted that mercurochrome-220 soluble, which is closely akin to eosin, did stain cartilage uniformly. This point will be discussed again.

The dyes chosen were also injected into six knee joints of three rabbits. A 1 per cent solution of isamine blue was used in one knee; the joint was examined one week later. A 1 per cent solution of mercurochrome was used in one case; this joint was examined one week later. A 1 per cent solution of gentian violet was injected into two joints; the knee joints were examined three and nine days later, respectively. A 1 per cent solution of methylene blue was injected into two knee joints. Examination was made three and nine days later, respectively.

No attempt was made to change the strength of solution previously used. All these dyes stained normal, healthy cartilage. It was noted that the intensity of staining diminished as the dye remained in the joint longer, the dye being distributed unevenly. In the case of gentian violet, it was noted that the posterior part of the femoral condyles was still well stained three days after injection, but that the posterior compartment of the knee showed a bluish granular débris, a possible evidence of synovial irritation. In a joint into which injection of methylene blue had been made an accidental suppurative arthritis developed, confined to the anterior aspect of the joint. There was no suppuration in the posterior compartments, and the dye was still present over the posterior part of the femoral condyles. Synovia and other intra-articular structures stained well, especially with gentian violet.

It is thus seen that the immediate effect of these dyes is a uniform, superficial staining of cartilage and synovia, without particular irritation. All parts of joint cartilage do not stain equally well, those more accessible to the dye staining better. Thus the tibial condylar cartilage usually did not stain well. As time passed, and even as early as the second or third day after injection, there was a gradual disappearance of the dye from the joint, so that no dye or possibly only patchy areas of dye-stained cartilage were present. All the dyes used, in the particular concentrations noted, stained cartilage uniformly, and there was no selectivity of staining.

*Effect of Dyes on Experimentally Traumatized Joints.*—Into eighteen knee joints of nine rabbits various dyes were injected as tabulated (table), the joints having been traumatized experimentally as previously described. At varying intervals after the initial trauma, the dye chosen was injected into the joints. The joints were opened at once to determine the effect of the dye, with particular reference to selectivity of staining.

It is not necessary to go into any detailed gross and microscopic examination of these traumatized joints. The work agrees in general

with the results reported by Key. Whether the alterations within the joint produced by trauma can be strictly called arthritis is an important point, especially from the standpoint previously enunciated that natural arthritic erosions stain selectively. Usually, synovial hypertrophy and synovial adhesions were present; in some cases, the synovial adhesions were so marked that it was not possible to inject the dye into the joint. The areas of damage originally inflicted by the needle either were superficial or reached to the bone marrow. Many of the lesions, especially the more recent ones, were covered with fibrin. There was no tendency toward repair of these traumatic defects in cartilage or toward enlargement of these areas. In some cases, as noted by Key, there was a tremendous overgrowth of one or both condyles of the femur, so

*Duration of Traumatic Change in Knee Following Injection of Dye into Traumatized and Normal Joints*

Dye Used	Per Cent	Days	Dye Used	Per Cent	Days
Eosin.....	*0.025.....	39	Trypan blue...	0.2.....	28
	0.02.....	28		0.5.....	35
	0.05.....	51			
	*0.05.....	39	Neutral red....	0.1.....	33
	0.1.....	51		2.....	At once
	0.1.....	33	Janus green....	0.2.....	39
	0.5.....	34	Safranin O....	1.....	45
	2.....	49			
	2.....	At once	Alum carmine..	1.....	45
Mercurochrome	0.05.....	35	Allizarin.....	Saturated solution..	41
Isoamine blue...	1.....	49	Aniline blue....	0.1.....	41

\* Injections were made into the normal hip joints.

that laterally or medially they projected as large, irregular, bony masses. This condition was present only in the severer cases. In many cases there was an irregular, linear, osteophytic overgrowth of the ridges bordering the upper part of the intercondyloid fossa. In a few cases, defects in the tibial condylar cartilage were present, though more often a tear in the semilunar cartilage was noted. In only one case was a pedicled cartilaginous foreign body present. This is in accord with the experience of Moulouguet,<sup>7</sup> who noted that traumatic, experimentally detached, cartilaginous bodies were resorbed, unless pedicled.

The circumstances, then, are possibly not favorable for a selective staining of cartilage, as previously described in areas of natural arthritic erosion in cadavers. Fresh fractures in cartilage surely do not stain selectively. In no case, and with no dye used, was there a selective staining of these artificial areas of cartilaginous defect. In a few cases it was not possible to inject the dye into the joint, but in all joints in

7. Moulouguet, P.: Foreign Bodies in Joints, J. Bone & Joint Surg. **11**:353, 1929.

which the dye was present, uniform staining of cartilage resulted, depending on the strength of the solution of dye used. In this respect, the behavior of eosin and mercurochrome is interesting. Two things were noted previously about eosin: (a) it did not stain normal cartilage and (b) it was a selective stain for naturally diseased areas in cartilage, especially erosions (in cadavers). Eosin and mercurochrome are considered together because of their intimate relation to each other. Both, be it noted, stain normal cartilage in solutions that are above 0.05 per cent; at that level or below, cartilage is not stained, but synovia is. Our dilutions previously used were not so accurate. This is true of other dyes, the intensity of staining depending on the strength of the solution of the dye. Neither eosin nor mercurochrome, however, showed any selectivity for artificially traumatized areas in cartilage, as produced here. This, of course, does not mean that eosin does not stain selectively; we have seen it do so. It only means that under certain conditions, and our experience is as yet too limited to define those conditions, eosin does stain selectively. This demands more extensive investigation.

Neutral red, previously indicated as possibly selective in action, stained cartilage uniformly in strengths above 0.1 per cent; there was no selectivity. Alum carmine stained uniformly. Trypan blue, as noted by Menkin,<sup>8</sup> is fixed by inflammatory areas, when injected directly into them or intravenously; it is not fixed when injected at the periphery of such an area of inflammation. When injected intra-articularly, it stained uniformly and not selectively. This type of injection, then, possibly corresponds to a peripheral injection.

It should be noted that areas of erosion took up the dye, but no more so than did normal cartilage. No immediate reaction of the joints to dyes was noted. No metachromasia was present, except possibly in the case of Janus green, in which the color gamut of the stained cartilage ran from violet to blue.

#### SUMMARY

The injection of various dyes into normal joints and into joints experimentally traumatized produces an immediate, uniform, superficial staining of the cartilage of the joint. The artificially diseased areas in cartilage do not take up the stain selectively. No ill effect in the joints from the injection of dye in solutions of the strengths used was noted. If the dye is permitted to remain in the joint, it is absorbed, usually within a week.

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8. Menkin, V.: An Aspect of Inflammation in Relation to Immunity, *Arch. Path.* **12**:802 (Nov.) 1931; Studies on Inflammation: VI. Fixation of Trypan Blue in Inflamed Areas of Frogs, *J. Exper. Med.* **53**:179, 1931.

# FIFTY-FIRST REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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## CONGENITAL ABNORMALITIES

*Amniotic Origin of Deformities of the Limbs.*—Hellner<sup>1</sup> studied a series of congenital malformations and amputations. He concluded that while amniotic bands could have been the cause of some of the deformities, defects in the mesenchymal tissue had to be considered as a cause in others. Absence of limbs could be produced experimentally by intra-uterine ligation of the limbs of embryos. To accomplish this it was found necessary to interrupt the circulation completely. Fractures in utero healed much as in extra-uterine life. While fibrous union of fractures was observed in a few instances, its frequency did not seem unusual to the observers.

*Congenital Paramyotonia.*—Urechia and his co-workers<sup>2</sup> reported a case of paramyotonia. This disease was characterized by rigid contractures of one or more limbs excited by temperature changes or other

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This report of progress is based on a review of 179 articles selected from 265 titles dealing with orthopedic surgery appearing in the various medical journals approximately between Nov. 26, 1932, and March 20, 1933. Only the publications which seemed to represent progress have been selected for review.

1. Hellner, Hans: Arch. f. klin. Chir. **172**:133, 1932.

2. Urechia, C. I.; Retezeanu, A., and Dragomir, L.: Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1430, 1932.



stimuli. These contractures lasted from a few minutes to several hours and were followed by a flaccid paralysis lasting several hours. There was no true tetany. The patient was a girl of 15 whose grandmother had suffered from the same disease for twenty years. The girl had been normal until 4 years of age, since which time she had developed very slowly. She complained of painful cramps in both upper and lower limbs, lasting from one-half to two hours, followed by a feeling of weakness in the affected limb. There were no reflex or sensory changes present. Blood calcium was determined during and between attacks and was found to be 6 mg. per hundred cubic centimeters. Accordingly, parathyroid extract was administered daily for a week. The cramps persisted but were not so severe, and the blood calcium rose to 7.5 mg. per hundred cubic centimeters. After another week the blood calcium reached normal, and the cramps disappeared. No treatment was then given for ten days, at the end of which time the blood calcium had fallen to 7 mg. per hundred cubic centimeters, and the cramps returned. Treatment was therefore kept up at regular intervals. Coincidentally with this treatment, the patient grew very rapidly, put on weight and began to menstruate. The authors also reported the case of another patient in whose family paramyotonia had been present for four generations.

*The Hip Joint from a Roentgenologic Standpoint.*—Morrison<sup>3</sup> made a complete study of the development, from birth, of the epiphyses concerned in the formation of the component parts of the hip joint. Of greatest significance was his description of the anterior, superior and posterosuperior epiphyses of the acetabulum. He pointed out that the Y cartilage between the iliac, pubic and ischial portions of the acetabulum was a genetic center and grew in such a manner that it controlled the final width of the acetabulum. On the other hand, the superior three acetabular epiphyses controlled the depth of the acetabulum. The latter epiphyses appeared at about 12 years of age and fused with the acetabulum between the sixteenth and eighteenth years. Failure of fusion of these epiphyses resulted in the frequently seen ossicles in this area. Failure of development or absence of these superior acetabular epiphyses were held to be the etiologic factor in congenital dislocation of the hip. Following early reduction of congenital dislocation of the hip, if these epiphyses were absent, the acetabulum failed to deepen and redislocation occurred.

[ED. NOTE.—The studies of Morrison afford an interesting contrast to the views of Calot, who believes that a subluxation of the femoral head is the cause of the shallow acetabulum. Evidence may be adduced for both views.]

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3. Morrison, L. B.: Am. J. Roentgenol. 28:484, 1932.

## DISTURBANCES IN OSSIOUS METABOLISM

*Magnesium Rickets.*—Meyer zu Horste,<sup>4</sup> in experimental work with rats, found that a marked increase in the magnesium of the diet produced rickets of the same pathologic picture as that produced with diets poor in calcium, when a diet low in phosphate was used. He reviewed the literature in which it was observed that there was an increase in the magnesium content of bone in rickets and in osteomalacia. The author expressed the belief that the magnesium hindered the process of calcification in bone.

*New Treatment for Rickets.*—Bloom<sup>5</sup> reported that the addition of secondary calcium phosphate to the diet of children could prevent and cure rickets without the aid of vitamin D.

[ED. NOTE.—This abstract is given because it represents a radical departure from previous hypotheses concerning the etiology of rickets. A need of substantiation of the author's findings seems indicated.]

*Changes in Bone and Photocystocol Toxicosis.*—Gottche and Kellner<sup>6</sup> studied the osseous changes in rats in intoxication due to viosterol. Osseous changes were observed in 19 of 106 rats which were given large doses of viosterol. In only 7 were the changes demonstrable by roentgenograms. The authors found that the osseous system was involved late, the order of frequency of involvement in this series being kidneys, aorta, stomach, lungs, muscles, glands of internal secretion and lastly bones. The bones showed gradually increasing atrophy. Microscopic examination showed the porosis of the cortex and trabeculae seen in the roentgenogram. There was narrowing of the epiphyseal cartilage bone. Porosis of the bone plus osteoid formation was the outstanding change. A summary of the literature was given.

*Osteomalacia.*—Wilson<sup>7</sup> investigated the treatment of osteomalacia (late rickets) by the daily administration of 1 drachm (3.75 cc.) of precipitated tricalcium phosphate. It was found that if the patients were able to walk about or work in the sunlight, healing took place in six weeks. If they were crippled and could only sit in the sunlight, there was no improvement. If they were kept indoors and deprived of both sunlight and adequate diet, whether they were crippled or could walk, almost no healing took place until vitamin D was given. It was suggested that muscular and circulatory activity in addition to sunlight could bring about an action similar to that of vitamin D.

4. Meyer zu Hörste, G.: *Klin. Wchnschr.* **11**:1796, 1932.

5. Bloom, C. J.: *South. M. J.* **25**:1109, 1932.

6. Gottche, O., and Kellner, B.: *Arch. f. Kinderh.* **97**:76, 1932.

7. Wilson, D. C.: *Indian J. M. Research* **20**:387, 1932.

Treatment of Osteomalacia with Viosterol: Decourt and Kaplan<sup>8</sup> believed that osteomalacia was not recognized as a rule until the bony changes and symptoms were so pronounced that the diagnosis was obvious. Early cases in which there were no symptoms and in which bony changes were not evident were manifested in a general physical asthenia without the cause being suspected. The disease could exist in a quiescent or abortive state. The good results following the use of viosterol in rickets led the authors to try it in cases of osteomalacia. They claimed no priority for this treatment but quoted from other authors who had tried the drug with success. The writers concluded that although osteomalacia responded well to viosterol, the disease could not be regarded as a simple avitaminosis. The need of vitamin D was thought to be associated with an endocrine disturbance of some sort.

*Osseous Dystrophy Following Icterus Gravis Neonatorum.*—Braid<sup>9</sup> described a case of a child who had icterus gravis neonatorum for several months, and who, between the second and third years, was found to have cystic conditions in the long bones. These abnormalities were limited to the diaphyses, and presented the same roentgenographic appearances under various forms of treatment during the subsequent years. Similar appearances had been noted in the long bones of puppies which had had their bile ducts occluded experimentally. Braid suggested that the explanation did not lie in the fact that the fat and calcium were less readily absorbed from the intestine in the absence of bile, but rather in that the retention of bile had impaired the functional capacity of the liver. He considered that possibly the liver is responsible for the distribution of vitamins A and D, which are so important in normal ossification.

#### NEOPLASMS

*Hemangioma of a Vertebra.*—Ireland<sup>10</sup> reported a case of hemangioma of a vertebra and gave summaries of 13 cases previously reported in the literature. He noted that 393 cases of hemangioma of a vertebra had been discovered at necropsy and had not given clinical symptoms. In all, the symptoms were insidious in onset, and were chiefly weakness, ataxia and spasticity. Pain was not an outstanding symptom. There was usually tenderness over the involved vertebra. The lesion was usually confined to a single vertebra, and the disk was not involved. The lower thoracic or lumbar vertebrae were usually affected. The diagnosis was made chiefly by roentgenogram. Differential diagnosis

8. Decourt, J., and Kaplan, S.: *Paris méd.* 2:485, 1932.

9. Braid, F.: *Arch. Dis. Childhood* 7:313, 1932.

10. Ireland, J.: *Am. J. Roentgenol.* 28:372, 1932.

was often difficult. Treatment of the hemangiomas had consisted of roentgen therapy or application of radium; the latter was preferred by the author.

*Benign Angiomatous Tumors of the Skeletal Muscles.*—Two hundred and fifty-six reported cases of benign angiomatous tumors of the skeletal muscle were reviewed by Jenkins and Delaney,<sup>11</sup> and 62 of them were summarized in tabular form. Such tumors were found to occur in the first half of life and usually before 20 years of age. The etiology was not established. The usual symptoms were a slowly growing mass in the muscle tissue accompanied by a varying amount of pain, tenderness and functional disability. The tumor occurred most frequently in the extremities, especially the thighs. It was found to be diffuse more often than circumscribed. Operative removal was therefore extremely sanguineous and sometimes seriously so. Diagnosis was seldom made before operation. Findings pointing to a correct diagnosis were the recovery of blood by aspiration and the presence of phleboliths on roentgen examination. Microscopically, the tumors were found to have a cavernous structure filled with normal blood. Arteries, veins and capillaries were frequently present. In the stroma of connective tissue degenerative fibers of skeletal muscle were encountered, and this degenerative process was usually complete in the center of the tumor. Prognosis after surgical removal was found to be good. No deaths were reported. Incomplete removal of the tumor resulted in recurrence in several cases.

*Malignant Giant Cell Tumor of Bone.*—Methods of differentiating between benign and malignant giant cell tumors of bone were discussed by King,<sup>12</sup> and a report of a case of the malignant variety was given in detail. The typical histologic appearance of the malignant tumor was that of a very cellular stroma comprised chiefly of spindle cells with active nuclei and occasional mitotic figures. Tumor giant cells might not be present. If, however, in such a tissue infection, bone destruction or hemorrhagic degeneration occurred, the local picture changed, showing foreign giant cells and a pleomorphic stroma, both strongly suggestive of the innocent tumor. It was therefore obvious that if a portion was taken for histologic examinations it had to be removed from an area where no inflammatory or degenerative process was present. A very thorough examination had to be made of several sections, and the most valuable criterion of malignancy was taken to be the presence of mitotic figures. Roentgenographically, in the malignant variety, involvement of the cortex was seen and later a growth into the soft tissues.

11. Jenkins, H. P., and Delaney, P. A.: Surg., Gynec. & Obst. **55**:464, 1932.

12. King, E. S. J.: Brit. J. Surg. **20**:269, 1932.

had a metastatic tumor only in one vertebral body. In carcinoma of the cervix and ovary, metastatic tumors in bone were observed only in about 2 per cent of the cases. Osseous metastases were rare in carcinoma of the stomach and in melano-epithelioma. In abdominal carcinoma, metastases were not common. When they occurred, they were usually osteoclastic. In carcinoma of the colon, osseous metastases were usually found in the spine. Metastatic tumors of any kind observed in the spine were usually central in origin. In the vertebral body there was no involvement of the disk, evidence of bony proliferation or enlargement of the vertebra.

*Bone Metastases from Carcinoma of the Breast.*—In a study of 106 cases of cancer of the breast, Downs<sup>19</sup> found osseous metastases in 33 per cent. The occurrence given in the literature varied from 5 to 53 per cent. The bones most frequently involved were the femora, pelvis, ribs, lumbar spine and skull, in the order given. The average time between the recognition of the tumor and the discovery of metastases in bone was four years and eight months. Of 57 patients with metastases, visceral as well as osseous, 44 were dead. A study of pathologic material did not confirm the statement by Copeland that most mammary carcinoma with metastases to bone was scirrhus. Scirrhus carcinoma was found in only 33 per cent of the cases with metastases to bone.

#### POLIOMYELITIS

*Drinker Respirator in the After-Cure of Infantile Paralysis.*—Legg<sup>20</sup> reported his observations on the use of the Drinker respirator in cases of infantile paralysis treated by the Harvard Infantile Paralysis Commission. He used it not only during the acute stage of the disease as a life-saving measure, but also later as a passive exerciser of the muscles of respiration. Measurements of voluntary expansion of the chest taken on a series of patients who received regular daily treatment in the respiration machine over a period of months showed a definite and steady increase from amounts under  $\frac{1}{2}$  inch (1.27 cm.) up to 2 and 3 inches (5 and 7.6 cm.) of voluntary expansion away from the machine. Consequently, the extreme deformities of the chest commonly observed in extensive paralysis were for the most part prevented.

*Drinker Respirator in Respiratory Failure in Poliomyelitis.*—Wesselhoeft and Smith<sup>21</sup> reviewed 30 cases of respiratory failure following infantile paralysis in which the Drinker respirator was used. Thirteen of the 30 patients survived owing, in the authors' opinion, wholly to the

19. Downs, E. E.: J. M. Soc. New Jersey **29**:957, 1932.

20. Legg, T.: Use of the Drinker Respirator in After-Care of Infantile Paralysis, J. A. M. A. **100**:647 (March 4) 1933.

21. Wesselhoeft, C., and Smith, E. C.: New England J. Med. **207**:559, 1932.

#### TUBERCULOSIS

*Tuberculosis of the Bones and Joints in Children.*—Hyde<sup>23</sup> reported that during the past ten years 4 per cent of all applicants to Springfield Lake Sanitarium, Ohio, have had definite tuberculosis of the bones or joints whereas 5 per cent of the 1,220 children among the applicants were so afflicted. Thirty-nine per cent of the cases originated before the sixth year, and 57 per cent before the sixteenth year. Tuberculosis of the bones and joints was usually the result of metastases from disease in the lungs or lymph nodes. The metastases were often blood-borne, and multiple lesions involving various organs or tissues might develop. An average of 2.6 tuberculosis lesions per patient was found in this group. The site of metastasis was favored by injury and local disturbances of nutrition. Twenty-seven per cent of adults and children gave a history of injury. The average duration of the disease in this series of children, including all types of bone and joint lesions, was about five years. The author felt that this period could have been shortened practically one-half had earlier diagnosis been made, adequate treatment given and unwise surgical intervention been omitted. Conservative treatment was the method of choice for children: "orthopedic

22. Howitt, B. F.: J. Infect. Dis. **51**:565, 1932

23. Hyde, C. L.: Am. Rev. Tuberc. **26**:625, 1932.

rest, adequate diet, heliotherapy and open air life; the first two therapeutic procedures being of greatest importance. Surgical measures were not to be considered until the disease had become quiescent or arrested.

[ED. NOTE.—This excellent article merits careful reading and consideration. Emphasis placed on the general care of the tuberculous bones or joints to the exclusion of a single method of therapy is the only accepted method of treatment. Early operative therapy is often followed by disaster.]

*Positive Pressure in Arthrodesis for Tuberculosis of the Knee Joint.*  
—Key<sup>24</sup> observed that a certain number of tuberculous knee joints failed to obtain bony ankylosis in spite of complete excision and prolonged immobilization. To secure ankylosis more surely, he devised a method of maintaining positive pressure between the excised ends of bone. A Steinman pin was inserted through the lower end of the femur and another through the upper end of the tibia. The pins were connected by turnbuckle screws. Immobilization was secured by a plaster cast from toes to groin. Constant pressure was maintained by the turnbuckle screws. Bony union was usually found in eight weeks. Unprotected weight-bearing was permitted in sixteen weeks.

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24. Key, J. A.: South. M. J. **25**:909, 1932.

(To be continued)

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## SPONTANEOUS RENAL AND URETERAL FISTULAS

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CLEVELAND

Renal and ureteral fistulas are uncommon, and when encountered usually are the result either of traumatic injuries or of surgical accidents. The spontaneous development of such urinary fistulas is so rare as to demand notation. Cases of nephrocolic, nephroperirenal, nephrochylous, ureterovesicoperitoneal and ureteroperiureteral fistulas have been studied at the Cleveland Clinic, all of which were the result of advanced pathologic processes which permitted the extravasation of urine into the adjacent organs and tissues.

Spontaneous renal and ureteral fistulas are unusual; their etiology is interesting, and they present difficult therapeutic problems; hence the following case reports.

### REPORT OF CASES

CASE 1.—A woman, aged 21, was admitted to the Cleveland Clinic in January, 1929, because of pain in the left flank. For three years she had had recurrent attacks of "blind boils" over the anterior surface of the tibiae. The nodules had been sore and painful but had not ulcerated. Each crop had lasted for a period of one month, and then had subsided spontaneously.

Six weeks before coming to the clinic she had noticed pain in the left lumbar region radiating down the posterior aspect of the left thigh to the knee. At that time, the patient had been hospitalized for one week and had been told that she had "kidney disease." She complained of nocturia—four or six times—with urgency and burning on urination. She said that the urine was always cloudy and sometimes resembled milk. For two weeks the pain in the left lumbar region had become more intense, and the patient walked with a peculiar gait due to the inability to extend the left thigh completely. She had profuse night sweats, fever and occasional chills.

The physical examination revealed an asthenic, malnourished woman, apparently suffering from some chronic disease. Examination of the head, chest and heart gave essentially negative findings. The abdomen was symmetrical. Marked tenderness was present over the left costovertebral angle and flank. The muscles of the iliolumbar group were spastic and rigid, but extreme tenderness in this region precluded palpation of the kidney or detection of a perirenal mass. The pelvic organs were normal. The patient held the left thigh in a semiflexed position, and attempts to extend it fully caused pain in the left lumbar area. There were numerous small, firm, tender, erythematous nodules about 4 to 10 mm. in diameter scattered over the anterior surface of both tibiae. The temperature was 100 F.; the pulse rate, 126, and the blood pressure, 90 systolic and 58 diastolic.

From the Cleveland Clinic.



The red blood cells numbered 3,580,000; the white blood cells, 19,300, and the hemoglobin was 91 per cent. The blood sugar was 73 mg. and the urea 27 mg. per hundred cubic centimeters of blood. Serologic studies and repeated blood cultures gave negative findings.

Cystoscopic examination revealed a slight subacute cystitis. Both ureters were catheterized readily, and urine from the right kidney was normal, while a specimen from the left side was loaded with pus and *Bacillus coli*. All studies failed to show the presence of tuberculosis. In the differential renal function test the indigo carmine appeared on the right side in a concentrated form in five minutes, but none appeared on the left side in fifteen minutes.

A pyelogram of the left kidney showed a large, irregular, fragmented pelvis with extravasation of the pyelographic medium from the lower pole of the kidney

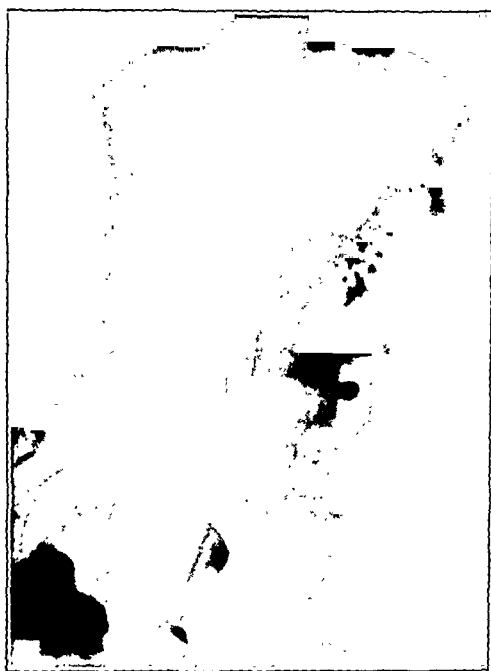


Fig. 1.—Pyelogram showing a large, irregular, fragmented pelvis with extravasation of sodium iodide from lower pole of left kidney into the colon, suggesting a nephrocolic fistula with coexisting perinephritic abscess.

into the colon (fig. 1). A diagnosis of a nephrocolic fistula with a coexisting perirenal abscess was made.

The patient was admitted to the hospital that evening, and because of her toxic condition she was given a transfusion of 500 cc. of blood. At operation on the following morning a large perinephritic abscess surrounding the left kidney was found, and 10 ounces of thick, foul-smelling pus escaped, cultures of which contained *Bacillus coli*. The kidney was enlarged and boggy. Most of the cortex had been destroyed by an active intrarenal infection. The patient's condition was too critical to permit a primary nephrectomy, so the perirenal abscess was drained.

Convalescence was uneventful until the ninth day after operation, when the temperature rose to 102 F. As this febrile reaction continued for eight days, it was thought that there might be a circumrenal collection of pus that was not draining.

Hence, the sinus tract was explored, but no pus was found. It appeared that the infection must be confined to the kidney. However, the patient continued to have fever, failed to gain in strength and did not improve sufficiently to undergo nephrectomy. She was discharged from the hospital, and a high vitamin diet, sun baths and absolute rest were advised. Improvement was very slow, and two years later she had a recurrence of pain in the left lumbar area, associated with fever, chills, pyuria and tenderness over the left kidney. At another hospital, a large perinephritic abscess was incised and drained.

During the next three months the patient improved considerably, and gained about 15 pounds (6.8 Kg.) in weight. For the third time she had a recurrence of pain over the left kidney associated with the classic signs and symptoms of a perirenal abscess. She was hospitalized, and Dr. Herrick explored the left kidney. He encountered a large perinephritic abscess which was drained. There was considerable difficulty in mobilizing the kidney, as it was firmly adherent to all perirenal structures. Extending from the renal pelvis to the splenic flexure of the colon was a firm band of fibrous tissue, which, on being severed, permitted a small amount of gas to escape from the bowel. Careful dissection showed this connective tissue strand to be a fistula which opened into both the colon and the renal pelvis. The opening into the bowel was closed by an inverted stitch and the kidney was removed.

In spite of the fact that all preoperative examinations had failed to show any evidence of acid-fast bacteria, microscopic studies of the kidney demonstrated areas of tuberculous ulceration. The patient improved considerably following the nephrectomy, but the last report stated that she was having urinary disturbance due to tuberculous cystitis and perhaps an involvement of the right kidney.

This case of nephrocolic fistula was the result of chronic renal tuberculosis which is the most common cause of nephro-intestinal fistula. In this case the renal tuberculosis had persisted for three years.

CASE 2.—A man, 40 years of age, came to the clinic in December, 1930, complaining of "kidney trouble." He said that for the past sixteen years he had suffered recurrent attacks of severe colic in the left lumbar area, associated with fever, chills, pyuria and the passage of stones. Four years previously, the right testicle had become swollen, tender and slightly inflamed, and several small cutaneous sinuses had developed from which there had been a continuous purulent discharge. During the last four months there had been a constant, dull, aching pain in the left lumbar area associated with a sense of soreness and tenderness in the left costovertebral angle. He had nocturia about four times, always accompanied by a sense of incomplete evacuation of the bladder, urgency, tenesmus and burning on urination. Two weeks before he came to the clinic, swelling had appeared in the area of the left kidney, and since then he had been unable to extend the left thigh fully, as attempts to do so caused lumbar pains.

The patient had lost 32 pounds (14.5 Kg.) in weight during the past six months, in spite of a good appetite. He denied that he had had any pulmonary, cardiac or gastro-intestinal symptoms.

Physical examination showed an emaciated, asthenic man who walked with a peculiar limping gait, because of his inability to extend the left thigh fully. Examination of the throat, head, lungs and heart gave essentially negative findings. The abdomen was symmetrical, the muscles were atonic, and no tenderness or rigidity could be elicited. The temperature was 99.5 F.; the pulse rate was 120.

In the left costovertebral angle there was a fluctuant swelling. No definite mass could be outlined, but it seemed that a circumrenal collection of fluid was present. The skin overlying the tumefaction had a dusky red hue, indicating an inflammatory condition. No increase in local temperature could be detected.

The right epididymis was small, firm and indurated. When pressure was exerted on it, pus could be expressed from three cutaneous sinuses of the scrotum. Palpation of the prostate and seminal vesicles revealed no abnormality, and their secretions were normal according to microscopic evidence.

Laboratory reports were as follows: red blood cells, 4,380,000; white blood cells, 8,700, with a normal differential count; hemoglobin, 80 per cent; blood sugar, 70 mg. and urea 21 mg. per hundred cubic centimeters of blood. The Wassermann and Kahn reactions were negative in all antigens. The urine was loaded with

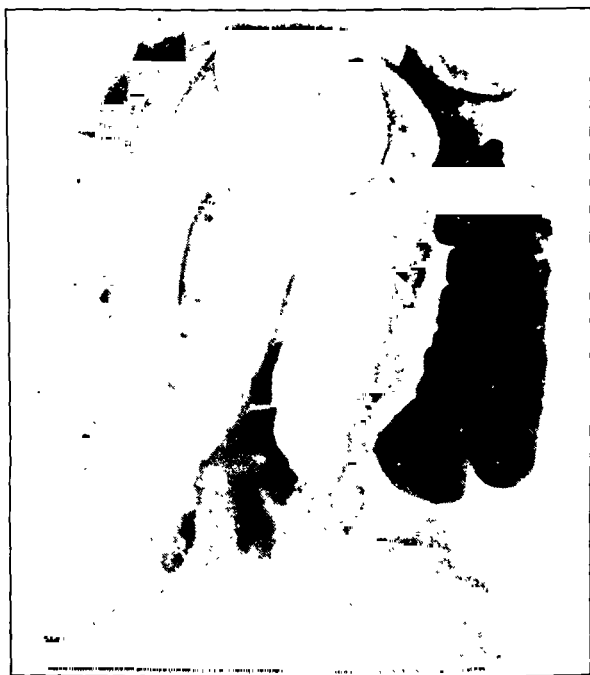


Fig. 2.—Pyelogram showing a nephrocolic fistula; barium is seen escaping from the splenic flexure of the colon and infiltrating the left perinephric region.

pus cells and contained numerous organisms, cultures of which revealed a mixed infection of *Bacillus coli* and staphylococci. All smears, cultures and animal inoculations of the sedimented urine were negative for tubercle bacillus. The renal function was good, as indicated by a 70 per cent excretion of the phenolsulphonphthalein dye administered by the intravenous method, and there was a normal range of specific gravity and concentrating power as shown by the Mosenthal test. Cystoscopic examination of the bladder indicated a slight inflammatory reaction of the mucosa but no definite signs of ulceration. In the differential kidney function test, the dye appeared from the right ureter, in a concentrated form, in four and one-half minutes; however, no dye was excreted by the left kidney in twenty minutes. Attempts were made to pass catheters and bougies up the left ureter, but an impassable obstruction was encountered about 1 cm. from the vesical orifice. Roentgenograms showed numerous areas of calcification in the left kidney which

suggested tuberculosis. Gastro-intestinal studies indicated that the stomach, duodenum and gallbladder were normal. An enema of barium sulphate filled the entire colon, and at the splenic flexure the barium escaped from the bowel and infiltrated the tissue around the left kidney (fig. 2).

The diagnosis suggested was nephrocolic fistula associated with perinephritic abscess.

Two days following the admission of the patient to the hospital, the fluctuant swelling in the left lumbar area ruptured spontaneously, a moderate amount of pus, undigested food particles and feces being discharged. It was hoped that by such drainage of the perinephritic abscess the patient's condition would improve; however, he continued to grow worse. Two days later, a second inflammatory swelling above the crest of the ileum in the left flank was incised, and a large quantity of foul pus was evacuated. Under a general medical regimen the patient improved slowly, but the failure of the urinary fistula to close and the persistent malodorous discharge, combined with a diseased, nonfunctioning left kidney indicated the necessity for operative intervention.

With the patient under spinal anesthesia, the left kidney was exposed, disclosing many dense perirenal adhesions. By careful dissection, it was possible to demonstrate a fistulous tract extending from the pelvis of the left kidney to the colon. The fistulous tract was excised, the opening in the colon was closed by two layers of inverted sutures, and nephrectomy was performed.

While the incision was being closed, the patient suffered acute shock. The respirations became rapid and shallow, and the pulse was weak, thready and almost imperceptible. The skin was cold and clammy. As an emergency measure, 500 cc. of whole blood and 300 cc. of 10 per cent solution of dextrose were given intravenously. The patient failed to respond to various measures of stimulation, and died about ten minutes after the incision had been closed.

At autopsy, multiple areas of ulceration were found at the splenic flexure of the colon and numerous small ulcers surrounded the ostium of the fistula. The parenchyma of the kidney was studded with multiple abscesses, but no gross or microscopic evidence of tuberculosis could be found. Examination of the right epididymis revealed a nonspecific inflammatory reaction.

Apparently the primary infection was intrarenal and was disseminated into the perirenal tissue, thus forming a perinephritic abscess. The abscess not only dissected its way into the colon but succeeded in forming a cutaneous sinus. Hence this case is typical for cutaneous, nephrocolic fistula.

CASE 3.—A man, 29 years of age, a truck driver, entered the Cleveland Clinic in February, 1925, complaining of pain over the "left kidney." For three years, he had suffered from recurring attacks of boils, the last crop having appeared about two months previously. During the last seven weeks he had noticed a sharp pain in the left lumbar area, associated with slight fever in the afternoon. The urine was cloudy, and the patient had passed several blood clots, although he denied that he had had a frank hematuria. There was no history of frequency or burning on urination, and no chills or passage of urinary calculi. For three weeks he had been confined to bed because of progressive muscular weakness. A review of the pulmonary, circulatory and gastro-intestinal symptoms gave negative findings. The family history was irrelevant.

Physical examination revealed an asthenic man. His temperature was 100 F., the pulse rate, 100, and the respiratory rate, 20. Examination of the heart, lungs

and abdomen showed them to be normal grossly. In the left costovertebral angle there was a definite sense of tenderness associated with a suggestive muscular rigidity. However, there was no fluctuation and no increase in local temperature, and no tumor could be detected by palpation. Neither kidney was palpable.

Investigations in the laboratory showed that the red blood cells numbered 3,880,000, the white blood cells, 16,000, and the amount of hemoglobin was 80 per cent. The value for blood sugar was 80 mg. and for the urea 36 mg. per hundred cubic centimeters of blood. Both ureters were catheterized with ease. A specimen of urine from the left ureter was loaded with pus cells and contained numerous bacilli, none of which was acid-fast. The urine from the right kidney showed no abnormality. Pyelographic studies revealed areas of calcification on the mesial side



Fig. 3.—Pyelogram showing a nephroperirenal fistula with an irregular fistulous tract leading from the left renal pelvis into the perirenal tissue.

of the left kidney with an irregular fistulous tract leading from the pelvis of the kidney out into the perirenal tissue (fig. 3). Evidently the pyelographic medium escaped from the kidney out into a coexisting perinephritic abscess.

The presence of pyonephrosis with an associated perinephritic infection having been demonstrated, it was thought advisable to remove the left kidney. At operation a large perirenal abscess was found to surround the left kidney completely and to communicate by means of a fistula with the renal pelvis. The kidney was enlarged, the cortex was soft, and numerous abscesses were present. The renal pedicle was ligated, the kidney was removed, and the perinephritic abscess was drained. A careful microscopic examination failed to reveal any evidence of renal tuberculosis, and cultures from the perirenal and kidney abscesses were negative for acid-fast bacilli. Convalescence was satisfactory, and the patient was apparently well at the last report.

This case of nephroperirenal fistula apparently represents the so-called metastatic kidney infection, the primary focus being probably the "cutaneous boils." The existing pyuria was caused by the rupture of the perinephritic abscess into the renal pelvis.

CASE 4.—A woman, aged 46, entered the Cleveland Clinic in April, 1925, complaining of pain in the left lumbar area. Eight months previously, she had suffered from influenza which she said had "settled in her kidneys." Since then she had suffered from recurring attacks of colic which always was localized in the left renal area. The pains were initiated by working, the attacks lasting for one or two days, and almost always morphine was required for relief. At times the



Fig. 4.—Pyelogram showing a ureteroperiureteral fistula; there is a duplex kidney pelvis with irregular nodular calices. At the level of the left sacro-iliac joint, a loop of the ureter deviates toward the vertebral column, and at this point the pyelographic medium escaped from the ureter and infiltrated the periureteral tissues.

patient suffered from urgency, frequency and burning on urination. Pus, albumin and occasional red blood cells had been found in the urine. She had had no frank hematuria and had never passed urinary calculi.

During the three weeks prior to her admission to the hospital, the attacks of "kidney pain" had increased in severity and frequency, being associated with nausea, vomiting, chills and mild fever each afternoon. She had no desire for food, and had lost 50 pounds (22.7 Kg.) in weight during eight months.

Physical examination revealed that the patient was greatly emaciated. There was no evidence of acute pain, and all mental processes were normal. Examination of the heart and lungs gave negative findings. On inspection, a definite fulness was found just beneath the left costovertebral angle with a decreased excur-

sion of the diaphragm on that side. The left iliolumbar muscles were very spastic, and the entire area was very tender. No definite mass could be detected because extreme tenderness precluded a careful examination. The skin was normal, and no evidence of fluctuation or abscess formation could be detected. Her temperature was 101 F., and the pulse rate was 110.

Red blood cells numbered 3,470,000, the white blood cells, 18,300, and the hemoglobin value was 65 per cent. The blood sugar was 87 mg. and the urea 39 mg. per hundred cubic centimeters of blood. A catheterized specimen of urine from the left kidney was loaded with pus and contained many nonacid-fast bacilli, while the urine from the right kidney was normal. The combined renal function according to the intravenous phenolsulphonphthalein test was 55 per cent in two hours.



Fig. 5.—Chronic pyonephrotic kidney with multiple cortical abscesses, one of which ruptured, permitting the urine to escape from the kidney into the perirenal space.

A pyelo-ureterogram of the left kidney and ureter showed a duplex pelvis with irregular nodular calices, and the two ureters were united before entering the bladder. At the level of the left sacro-iliac joint, a loop of ureter deviated toward the vertebral column, and at this point the pyelographic medium escaped from the ureter and infiltrated the periureteral tissue (fig. 4).

The foregoing findings suggested the preoperative diagnosis of duplex kidney with pyonephrosis associated with ureteral-periureteral fistula.

On exposure of the left kidney, a large perinephritic abscess was found from which 10 ounces of pus escaped (fig. 5). The kidney was about four times the normal size, and the cortex was soft and riddled with multiple abscesses. Three hundred cubic centimeters of thick pus was aspirated from the renal pelvis in order to expedite a nephrectomy. The perirenal abscess had extended along the ureter, and at the level of the left sacro-iliac joint a large periureteral abscess was found.

This abscess cavity contained pyelographic solution, but the fistulous tract could not be isolated on account of the pronounced inflammatory reaction of all the peri-ureteral tissue. However, the ureteral sinus was visualized by the pyelo-ureterogram, and the extravasation of the urographic fluid clearly indicated the presence of a ureteral fistula.

Convalescence was slow, but when the patient was last heard from she was enjoying good health.

This case illustrates the complications that may accompany pyonephrosis. The kidney was evidently the primary source of infection, and the inflammatory process extended to the perinephrium, producing an abscess. The perirenal pus dissected its way down the outside of the ureter, and at the junction of the middle and lower thirds it eroded the ureteral walls and evacuated its contents into the ureter, thus accounting for the coexisting pyuria.

CASE 5.—A laborer, 44 years of age, entered the Cleveland Clinic in October, 1930, complaining of "bladder trouble." He had been well until eight months before, when he had noticed a total hematuria which persisted for two weeks and then subsided spontaneously. Since then, the urine always had been cloudy. He had suffered from frequent urination, every two hours, associated with burning in the urethra. He denied lumbar pains and had never passed urinary stones. His general health had been good, but he had lost 10 pounds (4.5 Kg.) in weight during the last six weeks owing to voluntary restriction of diet. There was no familial history of tuberculosis.

The physical examination revealed that the patient was well nourished. His temperature was 98.6 F., the pulse rate was 76, and the blood pressure 136 systolic and 84 diastolic. His weight was 175 pounds (79.4 Kg.) (normal weight, 185 pounds [83.9 Kg.]). The only physical abnormality noted was slight prostatic enlargement. The gland was soft and boggy, and the secretion contained from 30 to 50 pus cells per high power field.

Cystoscopic examination revealed a chronic inflammation of the entire mucosa of the bladder, with localized areas of ulceration. The right ureteral orifice was surrounded with areas of bullous edema. Several obstructions suggesting multiple ureteral strictures were encountered in passing a spiral tipped catheter up to the pelvis of the right kidney. About 50 cc. of thick, cloudy urine was aspirated from the pelvis of the right kidney. The left kidney and ureter were normal. The indigo carmine dye was excreted from the right kidney in dilute form, in ten minutes, and from the left in concentrated form, in five minutes. Sixty per cent of the phenolsulphonphthalein dye was excreted in two hours.

Pyelographic studies indicated a chronic inflammation of the pelvis of the right kidney with cicatricial contraction of the lower calices and multiple strictures of the ureter. There were two definitely circumscribed shadows involving the lower end of the right ureter, which suggested the presence of diverticula. The pelvis of the kidney was irregular, and several small calcified areas were seen in the renal cortex. Dr. Nichols made the roentgenographic diagnosis of renal tuberculosis with a coexisting cystitis. However, catheterized specimens of urine were examined repeatedly before the presence of acid-fast organisms could actually be demonstrated.



On Nov. 16, 1928, nephrectomy was performed in a local hospital. Convalescence was uneventful, except that the wound refused to heal. Four weeks later the patient was admitted to the Cleveland Clinic. The temperature ranged from 98.6 to 103 F. The patient perspired freely, and complained of urgency and burning on urination. Approximately one half of his urine escaped through the right lumbar sinus in spite of the fact that the right kidney had been removed. Evidently there was a urinary fistula connecting the lumbar incision with the bladder. Cystoscopic examination failed to show such a fistula, but the bladder mucosa was so intensely inflamed and covered with punched-out ulcers that the examination was unsatisfactory.

During a long period of hospitalization, numerous therapeutic measures were employed in an attempt to control the hyperpyrexia and the cystitis and to facilitate closure of the incision, but all to no avail. The patient complained of tenderness in the right lower abdominal quadrant; the overlying muscles were spastic. He was very somnolent. His neck was stiff, and there was a bilateral ptosis of both eyelids. On March 30, 1929, seventy-five days after admission, he died from generalized miliary tuberculosis with signs of tuberculous meningitis.

The diagnosis of generalized miliary tuberculosis was confirmed at necropsy. The bladder was small and inflamed, and the mucous membrane was necrotic. The dome of the bladder on the right side was sacculated and communicated with a sinus tract leading to a large abscess located in the lower right abdominal cavity. The abscess contained a large amount of purulent material having an ammoniacal odor of decomposing urine. A second sinus connected the right ureter with the abscess cavity, and a third sinus joined the abscess with the lumbar wound. Thus the urine secreted by the left kidney escaped from the bladder by means of the vesicoperitoneal fistula or by going up the stump of the right ureter and escaping through the ureteroperitoneal fistula. It is true that the lumbar incision was caused by the previous operations, but the pelvic and the ureteral and vesical fistulas were of spontaneous origin. Examination of the right ureter revealed that the opening of the fistulous tract had been distal to the point of ligation during the previous nephrectomy. The entire pelvis and extravescical structures were involved in an extensive tuberculous inflammation, and the degenerative changes had so involved the wall of the ureter and bladder that they finally perforated.

The following case of urinary chylous fistula has been reported by Lower and Belcher of the Cleveland Clinic.<sup>1</sup> The case is summarized here in order to complete our present study.

CASE 6.—A Chinese cook came to the Cleveland Clinic in July, 1923, because of "bladder trouble." Five months previously he first had noticed that his urine was cloudy; at times it was so viscid and hazy that it resembled milk. There was no burning on urination, no urgency and no gross hematuria. During this period he had lost 10 pounds in weight, although his appetite was good. He had no pulmonary, cardiac or gastro-intestinal symptoms.

He was a native of China, but had lived in the northern part of the United States for ten years.

No gross abnormalities were noted on physical examination.

The blood count was normal, and no parasites were found, although repeated examinations were made at all hours of the day and night. Numerous blood

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1. Lower, W. E., and Belcher, G. W.: Chyluria: With a Report of a Case Treated with Neosalvarsan, *Surg., Gynec. & Obst.* **39**:147, 1924.

Wassermann and Kahn reactions were negative in all antigens. The blood sugar was 85 mg. and the blood urea 33 mg. per hundred cubic centimeters of blood.

The bladder was normal on cystoscopic examination. The urine collected from the right kidney was clear, while that obtained from the left side resembled cream. A chemical analysis of the urine by the Babcock method showed 1 per cent fat. The fat content was so high that its presence could be demonstrated grossly by its leaving a grease spot on absorbent paper. Repeated pyelographic studies during and between attacks failed to demonstrate any fistulous communication between the kidney and the lymphatic system.

The patient was given a course of neoarsphenamine, and the chyluria immediately subsided. However, he had severe recurrent attacks, and each time the urine gave a positive test for fat. The most unusual aspect of the case was the specificity to neoarsphenamine even though no *Filaria* were found.

While no fistulous tract was actually demonstrated, it seems logical to believe that there was an artificial communication between the lymphatics and the kidney which permitted the extravasation of the lymph into the urinary tract. Hampton<sup>2</sup> likened "the deep lymphatics of the kidneys to the cerebral arteries, as the points of lowest resistance in their respective systems and assumes that the lymphatic obstruction results in a leakage causing a chyluria just as hypertension often results in leakage which causes apoplexy."

From a study of the foregoing cases it is evident that renal and ureteral fistulas may result from a number of pathologic conditions; therefore, each type of fistula will be discussed separately and clinical examples will be cited from the literature.

#### RENAL FISTULA

Spontaneous perforation of the kidney accompanied by fistulous communication with adjacent organs or tissues usually is the result of advanced renal disease such as pyonephrosis, nephrolithiasis, neoplasm, tuberculosis or the various suppurative nephritides. However, the kidney may become damaged secondarily as a result of a ureteral obstruction with its coexisting hydronephrosis, or a perinephritic abscess may rupture into the renal pelvis, or a neoplasm of the bowel may extend and involve the kidney.

Renal fistulas may be classified according to etiology or according to their anatomic relationships, the latter being the most satisfactory classification, as the location of the fistula and organs with which it communicates are designated. We have followed the anatomic classification and have searched the literature for cases which represent the various etiologic processes.

2. Hampton, H. H.: Non-Parasitic Haemotochyluria. Bull. Johns Hopkins Hosp. 31:20, 1920.

*Nephroduodenal Fistula.*—Nephroduodenal fistulas are much less common than those of the gastronephric type, only three cases of the former having been reported in the literature. Rayner (cited by Chazet<sup>15</sup>) described a case observed by Campaignac, that of a tailoress, 45 years of age, who had noticed a swelling of the right flank. At times she suffered from intense nausea, and had vomited large amounts of foul, acrid, urine-like material. During the attacks of vomiting a spontaneous decrease in the size of the lumbar tumor occurred. Necropsy revealed a communication between the collapsed pyonephrotic kidney and the first part of the duodenum. Also two small sinus tracts joined the perinephritic abscess with the renal pelvis.

Bang<sup>16</sup> treated a patient who had renal and ureteral tuberculosis. The indurated ureter was partially occluded by the inflammatory process and produced a hydronephrosis which caused a fusion and finally an abnormal communication between the kidney and the duodenum. Fernelius presented an incomplete report of a duodenal-kidney fistula which he observed in 1646.

*Nephrocolic Fistula.*—Inflammatory lesions may produce communications between the kidney and any part of the large intestine. As a general rule, pyonephrosis, tuberculosis and perinephritic abscesses are the most common offenders.

Rayner described a case of renal tuberculosis in which a sinus tract joined the kidney and colon; two cutaneous sinuses also opened into the loin, forming a renocolic cutaneous fistula. Rayner referred to another example of tuberculous necrosis of the kidney and colon in which there was a patulous communication. D'Allaines and Rouffiac<sup>17</sup> treated a man who had a large tumor in the right part of the hypochondrium. An exploratory laparotomy revealed a large perinephritic abscess surrounding a kidney with caseous degeneration, the abscess having ruptured into both the kidney and the colon.

Ogle<sup>18</sup> observed a patient with a large perinephritic abscess which ruptured into the colon, causing a purulent diarrhea with expulsion of urinary calculi; the diagnosis was confirmed at autopsy. Morris mentioned the case of Ammundale,<sup>19</sup> who incised a large psoas abscess

15. Rayner, cited by Chazet, Gaston: Contribution à l'étude de la tuberculose rénale avec fistules, Thèse de Paris, 1899-1900, no. 374.

16. Bang, B. F. L.: Primaer tuberculose i urogenitalorganerne; kommunikation imellem duodenum og den højere ureter, Hosp.-Tid. Kjøbenh. 1:561, 1874.

17. d'Allaines and Rouffiac: Fistule pérenéphrocolique avec lésions inflammatoires du rein, Bull. Soc. anat. de Paris 93:324, 1923.

18. Ogle, J. W., cited by Weiser.<sup>30</sup>

19. Ammundale, cited by Morris.<sup>3</sup>

which was pointing in the lumbar area. Fifteen days later urine and feces were discharged from the incision. The psoas abscess was secondary to the calculous pyonephrosis.

External abscesses, arising from perforation of the kidney substance by a small stone, may open into the colon and discharge pus, urine and calculi into the intestinal tract, as observed by Rosenbach.

Dittrich<sup>20</sup> saw an appendicorenal fistula resulting from a ruptured appendix with a subsequent perinephritic abscess which perforated the kidney, thus forming a patulous tract between the kidney and the appendix. Cruveilhier<sup>21</sup> referred to a woman who was reported to have had a "septic death." At autopsy, both kidneys were found to be in the true pelvis and fused together behind the rectum. As a result of pyonephrosis, the infection had spread to the perirenal tissue and had formed an abscess which perforated the rectum, forming a renorectal fistula.

To this series may be added the two cases of nephrocolic fistula studied at the Cleveland Clinic. In one case the fistula between the kidney and colon communicated with a second sinus, which extended through the lumbar muscles, permitting undigested food to escape from the cutaneous opening.

*Renopulmonary Fistula.*—Communications between the kidney and the lungs, as suggested by the expectoration of pus, urine and urinary calculi, usually signify advanced renal disease. This is illustrated by tuberculosis of the kidney with its resulting perinephritis, which may lead to a perirenal abscess, the infection then spreading along the surface of the liver forming a subdiaphragmatic abscess which may perforate the diaphragm, producing an empyema, with final escape of the pus by erosion into one of the bronchi.

Morris referred to the case cited by Rayer, that of a locksmith, 39 years of age, who eighteen years before had had a stone removed from the bladder. For eight years he had suffered severe pains in the left lumbar area associated with sudden pyuria. The pains were sometimes referred along the course of the ureter. On two occasions a profuse purulent expectoration occurred with a simultaneous disappearance of the pyuria. Autopsy disclosed a communication between the bronchus of the lower left lobe of the lung and the kidney. The fistulous tract had extended through a dilated calyx, penetrating the diaphragm and opening into a bronchus: several small phosphatic concretions were lodged in the lumen of the sinus. The kidney was practically destroyed by tuberculous caseation.

20. Dittrich, cited by Weiser.<sup>20</sup>

21. Cruveilhier, cited by Morris.<sup>20</sup>

Roubier<sup>22</sup> and Pillet<sup>23</sup> each encountered a case of tuberculous nephritis in which erosion had occurred through the renal cortex, and the resulting perinephritic abscess had slowly bored its way through the diaphragm and had finally emptied into a bronchus. Hortels<sup>24</sup> reported a cold psoas abscess which evacuated itself by emptying into the renal pelvis, producing pyuria, and also opened into a bronchus causing a foul purulent expectoration. Gordon<sup>25</sup> described a case in which there was tuberculous infection of the kidney and a perinephritic abscess which ruptured into the lungs, associated with multiple ulcerated areas in the duodenum.

Van der Speck<sup>26</sup> treated a patient who coughed up thin purulent material containing urinary salts. When the patient expectorated a large quantity of this material, there was a simultaneous decrease in the size of the lumbar tumor. Urologic examinations indicated that this was a case of congenital dystrophy of the left kidney with a coexisting perinephritic abscess which had perforated the diaphragm and was draining into a bronchus.

Von Deesten<sup>27</sup> described a patient who coughed up a copious amount of foul purulent sputum whenever he lay down. Physical findings and roentgenograms of the chest were normal. A diagnosis of perirenal abscess was made. When the abscess was incised and drained, all pulmonary symptoms immediately subsided. Von Deesten believed this to be a case of renopulmonary fistula although the sinus tract was not actually demonstrated.

Spontaneous rupture of a large hydronephrotic kidney into the perirenal tissues may cause an empyema which perforates into a bronchus; in such a case Kondratovich<sup>28</sup> found pus and urine in the sputum. In 1910, McDwean<sup>29</sup> collected five cases of direct renopulmonary fistula, the majority being caused by tuberculous infection of the kidney.

*Renoperitoneal Fistula.*—Nontraumatic perforation of the kidney with extravasation of urine, pus and stones into the peritoneal cavity is rare, only six cases having been reported.

22. Roubier, C.: Tuberculous Kidney-Lung Fistula, *J. d'urol* **13**:195, 1922.

23. Pillet, cited by Weiser.<sup>30</sup>

24. Hortels, cited by Chazet.<sup>15</sup>

25. Gordon, S.: Case of Reno-Pulmonary Fistula with Ulceration of Duodenum, *Dublin Quart. J. M. Sc.* **41**:90, 1866.

26. Van der Speck, H.: Uroptysis, *Nederl. tijdschr. v. geneesk.* **2**:1855, 1923.

27. von Deesten, H. T.: Recumbent Posture Cough with Purulent Expectoration; An Indicative Symptom in a Case of Perinephritic Abscess which had Ruptured into a Bronchus, *J. A. M. A.* **88**:98 (Jan. 8) 1927.

28. Kondratovich, K.: Pyohydronephrosis with Elimination of Urine Through the Bronchus, *Med. Obozr., Moscow* **51**:591, 1899.

29. McDwean, cited by Weiser.<sup>30</sup>

Weiser<sup>30</sup> mentioned a case of calculous pyonephrosis which ruptured into the peritoneal cavity, producing localized peritonitis, splenic and subdiaphragmatic abscesses and empyema due to the infectious process spreading by way of the lymphatics to the pleural cavity. The infection also invaded the circumrenal tissue, producing a perinephric collection of pus.

Rupture of a kidney in which there has been long-standing hydronephrosis, and in which the walls of the renal pelvis have been stretched out to paper thinness, accounts for most urinary ascites. In the case reported by Bennett,<sup>31</sup> a ureteral stone had produced a progressive hydronephrosis which ruptured into the abdominal cavity. An immediate operation with aspiration of the urinary ascites and a repair of the ruptured kidney resulted in rapid convalescence. Taylor<sup>32</sup> referred to the case of a girl, 15 years of age, in whom a large cystic tumor extended from the left costal margin to the crest of the ilium. One night the cyst ruptured spontaneously, and on the next morning an exploratory laparotomy was performed, at which time urine was encountered in the peritoneal cavity. Since it was impossible to locate the artificial opening in the kidney, the hydronephrotic sac was sutured to the anterior abdominal wall, thus forming an external urinary fistula which permitted the continuous drainage of urine. On several occasions the ostium of the fistula closed, and immediately the patient had a recurrence of the kidney pain; as soon as the sinus tract was opened, the pain was relieved.

Turner<sup>33</sup> performed a laparotomy because of a ruptured hydronephrosis of a single kidney and found peritonitis due to urinary irritation and infection. Later, peritoneal abscesses developed, and the patient died. Bazy<sup>34</sup> has pointed out that if the urine is sterile, the resulting chronic peritonitis usually responds to surgical treatment, but if the escaping urine is infected, the patient rapidly succumbs to a fulminating peritoneal infection.

The diagnosis of urinary peritonitis is difficult, as attested by the following reports. Schreuder<sup>35</sup> performed an operation for appendi-

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30. Weiser, A.: Die nichttraumatischen Perforation und Fisteln des Harntraktes, *Ztschr. f. urol. Chir.* **28**:120, 1929.

31. Bennett, cited by Morris.<sup>2</sup>

32. Taylor, J. W.: Acute Hydronephrosis or Dilatation of the Pelvis of the Left Kidney: Rupture of Sac and Extravasation of Urine into Peritoneal Cavity; Operative Recovery with Rupture into Peritoneal Cavity, *Lancet* **2**:589, 1884.

33. Turner, Phillip: Hydronephrosis of Single Kidney: Spontaneous Rupture into the Peritoneal Cavity, *Proc. Roy. Soc. Med.* **16**:24, 1923.

34. Bazy, cited by LeComte.<sup>42</sup>

35. Schreuder, O.: Spontaneous Rupture of Hydronephrosis, *Deutsche Ztschr. f. Chir.* **191**:100, 1925.

citis and encountered free urine in the abdominal cavity due to a kidney ruptured by pyonephrosis. Tschugajeff<sup>36</sup> explored the abdomen for a cryptogenic peritonitis and was surprised to find a ruptured kidney with infected urine draining into the peritoneal cavity.

*Renoperirenal Fistula.*—The simplest and most common renal fistula is that caused by a rupture of the kidney which permits the extravasation of urine into the circumrenal tissue with the formation of perirenal and psoas abscesses. There are numerous pathologic conditions which might cause spontaneous rupture of the kidney.

It is not uncommon to find a perinephritic abscess which empties into the renal pelvis, causing intense pyuria. Alglave<sup>37</sup> encountered a case of tuberculous spondylolisthesis with an associated psoas abscess; the pus finally perforated the kidney, causing a sudden copious pyuria. In Weiser's patient the cold abscess developed from the dorsal vertebra and not only did it rupture into the kidney pelvis but the infection spread under the diaphragm, the bacteria reaching the pleural cavity by lymphatic dissemination resulting in empyema. Maudet<sup>38</sup> described a case in which there was a tuberculous kidney with multiple areas of caseation which finally perforated the kidney, and the infected urine infiltrated the perirenal tissues, causing a large perinephritic abscess. When the perinephritis is the result of a renal fistula, the pus usually collects posterior to the kidney. However, the fluid may be anterior to the kidney and push the peritoneum forward, forming a cystic mass which can be palpated through the anterior abdominal wall, and often is mistaken for an intra-abdominal tumor. Morris performed an autopsy on a patient who had died of scrofulous pyonephrosis and cystitis, and found a large retroperitoneal abscess which had dissected its way downward from the left kidney to the brim of the pelvis and the anterior crest of the ilium.

Vanwerts<sup>39</sup> cited the case of a woman, 25 years of age, who had undergone an operation for appendicitis, at which time a perityphlic abscess had been found and drained. Five days later urine was discharged from the wound. He felt that the perityphlic infection spread through the retroperitoneal tissue, causing a psoas abscess which ruptured into the renal pelvis. By the use of indwelling ureteral catheters, the patient made a satisfactory recovery. However, there is no certainty that the abscess did not perforate the ureter instead of the renal pelvis.

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36. Tschugajeff, cited by Weiser.<sup>20</sup>

37. Alglave, cited by Weiser.<sup>20</sup>

38. Maudet, cited by Chazet.<sup>15</sup>

39. Vanwerts, cited by Weiser.<sup>20</sup>

To this series of cases may be added our case 3 in which the perinephritic abscess eroded through the thin pelvic wall, giving rise to pyuria.

Spontaneous rupture of a hydronephrotic kidney is another cause of urinary extravasation into the circumrenal tissue. A persistent ureteral obstruction may produce a progressive hydrostatic dilatation of the renal pelvis to such a degree that it may rupture. Van Saar<sup>40</sup> observed an unusual case in which spontaneous perforation of the hydronephrotic kidney occurred twice. The first rupture of the renal pelvis permitted the urine to escape into the perirenal tissue, and under conservative treatment the patient made an uneventful recovery. Eighteen months later a severe pain in the area of the left kidney announced the second rupture. During the process of nephrectomy, urine was encountered in the perirenal tissue, and the rent in the pelvic wall was demonstrated in the removed specimen. Van Saar believed that the spontaneous healing of the renal pelvis following the first rupture was due to the sudden release of the intrapelvic pressure which permitted coaptation of the pelvic walls with consequent healing. The kidney tissue was functioning so slowly that the reparation was complete before sufficient fluid had collected to cause another rupture. The extravasated fluid consisted chiefly of water and sodium chloride; hence it was readily absorbed. Had the urine been infected, a perinephritic abscess probably would have resulted. An incarcerated calculus at the ureteropelvic junction may lead to a ruptured hydronephrosis and permit the urine to escape into the perirenal tissue. Mathe and Oviedo<sup>41</sup> observed such a case in which, following a pelviolithotomy and plastic repair of the perforation, the patient made an uneventful recovery. When the extravasated urine is mixed with sufficient blood to form a perirenal hematoma, as in LeComte's<sup>42</sup> case, the rent in the hydronephrotic kidney usually involves both the pelvic wall and the cortex. Wood<sup>43</sup> performed an exploratory laparotomy for an anticipated acute peritonitis and discovered a large cystic tumor surrounding the right kidney. He incised the mass, encountered free urine, and found a hydronephrotic kidney with a small opening into the pelvis whence urine had escaped.

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40. Van Saar, G.: Ueber Hydronephrosenruptur und den dabei auftretenden Symptomenkomplex, *Beitr. z. klin. Chir.* **64**:316, 1909.

41. Mathe, C. P., and Oviedo, G. F.: Spontaneous Rupture of Hydronephrotic Sax, Secondary to Ureteral Stone, *California & West. Med.* **26**:790, 1927.

42. LeComte, R. M.: Spontaneous Rupture of Hydronephrosis, *J. Urol* **15**:517, 1920.

43. Wood, W. F.: Spontaneous Rupture of Hydronephrosis, *Brit. J. Surg.* **10**:574, 1923.



Renal calculi generally are associated with chronic urinary stasis, infection and pressure necrosis, all predisposing to spontaneous perforation of the cortex of the kidney. If the stones are small, they may escape into the perinephric space and then migrate to the lower lumbar area, where they cause a psoas abscess, such as that observed by Pachkis.<sup>44</sup> However, a solitary, large dendritic stone may penetrate the cortical tissue and still remain lodged in the renal pelvis. Everett<sup>45</sup> performed a pelviolithotomy for such a condition, but the patient died from the absorption of infected urine.

Nephrolithiasis is usually associated with functioning renal tissue, and when the stone pierces the medulla and cortex, the extravasated urine may infiltrate all the perinephric tissue and produce pronounced constitutional reactions. Sometimes the escaping urine follows the course of the ureter, and a periureteral abscess may result, as was described by Turner.<sup>46</sup> Occasionally the urine dissects its way along the fascial and muscular planes, causing an inflammatory edema in distant areas. Heniline treated a patient with a tender inflammatory swelling of the scrotum, perineum and lower portion of the abdomen. Multiple incisions of the edematous area permitted the escape of foul material which resembled urine. At autopsy it was found that the upper calyx of the kidney had been perforated by a small stone, forming a nephroperirenal fistula. An unusual case of urinary extravasation was seen by Delzell and Harrah.<sup>47</sup> Their patient had a diffuse cellulitis of the penis, scrotum and thighs. The anterior abdominal wall and the lumbar muscles were involved in an extensive inflammatory reaction. The peritoneal cavity was filled with multiple abscesses, and the liver was pushed downward by a subdiaphragmatic collection of pus. The pleural cavity contained a localized empyema and was covered by a plastic exudate. This generalized systemic infection resulted from the spontaneous perforation of a pyonephrotic kidney.

A fourth cause for urinary extravasation into the circumrenal tissue is the spontaneous perforation of the renal cortex. Many cases of idiopathic rupture of the parenchyma of the kidney have been reported, but extravasation of urine was present in only a small percentage of these cases. The cortex of the kidney seems to be more friable than the pelvis and ruptures more frequently, but unless the

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44. Pachkis, R., cited by Weiser.<sup>30</sup>

45. Everett, William: Perforation of Kidney by a Large Branched Calculus, *Brit. M. J.* 1:17, 1925.

46. Turner, Alfred C.: Unusual Case of Urinary Fistula, *Lancet* 2:220, 1929.

47. Delzell, W. R., and Harrah, Frank W.: Eleven Cases of Ruptured Kidney, *J. Urol.* 18:131, 1928.

rent extends through all the cortical tissue and opens into the pelvis, or unless the entire kidney is split open, only perirenal hematoma is formed and no urine escapes.

Fox <sup>48</sup> described the case of a man, who on tripping and attempting to prevent falling, had performed some unusual muscular movements which caused pain in the right lumbar area. Exploration revealed a complete transverse rupture of the kidney with a perirenal hematoma mixed with urine. Many authorities are of the opinion that a kidney must be weakened by disease before it can be ruptured by muscular exertion.

In Brown's <sup>49</sup> case, two stones obstructed the ureter producing a pressure atrophy of the renal cortex which finally resulted in a rupture of the parenchyma of the kidney with liberation of urine into the perirenal tissue.

Rupture or perforation of the kidney substance may occur as the result of renal neoplasms, such as hypernephromas, carcinomas, embryomas or sarcomas. As the tumor growth is rapid, degenerative changes often result in necrosis of the renal tissue with the formation of urinary sinuses. Tuffier <sup>50</sup> described a case of renal carcinoma, and Hartmanns <sup>51</sup> cited the case of an unidentified neoplasm, both of which caused a spontaneous rupture of the cortex with urinary extravasation into the perinephrium.

*Renocutaneous Fistula.*—Renal fistulas which open exteriorly usually point in the loin, flank or groin. This type has received considerable attention in medical literature.

Tuberculosis of the kidney is the most frequent cause of cutaneous urinary fistula and represents advanced renal lesions. Barney and Mixter <sup>52</sup> treated a patient with renal tuberculosis complicated by an inguinorenal fistula, nephrolithiasis and transverse myelitis of the spinal cord.

Schwartz <sup>53</sup> encountered a tuberculous perinephritic abscess which not only produced pyuria by rupturing into the kidney but also caused

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48. Fox, O. E.: Ruptured Kidney Due to Muscular Action, *Atlantic M. J.* **31**:183, 1927.

49. Brown, R.: Spontaneous Rupture of Renal Pelvis, *Surg. Clin. North America* **10**:969, 1930.

50. Tuffier, M.: Hematome sous-peritoneal diffres par rupture spontanei d'un sarcome du rein, *Bull. et mém. Soc. d. chirurgiens de Paris* **32**:692, 1905.

51. Hartmanns, M.: Spontaneous Rupture of Cancer of the Kidney, *Bull. et mém. Soc. d. chirurgiens de Paris* **32**:695, 1905.

52. Barney, J. D., and Mixter, W. J.: Renal Tuberculosis Complicated by Inguinal Renal Fistula, Transverse Myelitis and Renal Calculus, *J. Urol.* **4**:391, 1920.

53. Schwartz, cited by Chazet.<sup>15</sup>

the development of a cutaneous fistula in the loin. Vright<sup>54</sup> discussed a case of advanced bladder and renal tuberculosis complicated by troublesome urinary sinuses which perforated through Petit's triangle. Broca,<sup>55</sup> Lucas<sup>56</sup> and Doyen<sup>57</sup> have mentioned instances of chronic urinary fistula opening in the loin as the result of caseous degeneration of the kidney.

Nephrolithiasis associated with pyonephrosis is often antecedent to perforation of the kidney; the stone is extruded into the perirenal tissue and finally escapes by burrowing its way through the skin. McClelland<sup>58</sup> described a case of ureterolithiasis which caused a renal fistula with two cutaneous openings; the first sinus opened into the loin and continued to discharge pus, urine and stones; four years later a second fistula opened through the groin, giving exit to pus and stones; both fistulous tracts healed following a nephrectomy. Weeks,<sup>59</sup> Gaston<sup>60</sup> and Whately<sup>61</sup> have cited cases of calculous pyonephrosis which terminated by the stones being expelled through the lumbar muscles. Crabtree<sup>62</sup> encountered a perinephritic abscess arising from a calculous perforation of the renal cortex, the escaping urine and pus spreading beneath the diaphragm causing a secondary subdiaphragmatic abscess.

Cutaneous renal fistula occurring as a result of a parasitic infection of the kidney is extremely rare. La Peyre<sup>63</sup> saw an unusual case in which the kidney had been converted into a fatty mass harboring three worms about  $3\frac{1}{2}$  inches (8.9 cm.) in length (the type not described). Several worms were found embedded in the perirenal tissue, and a sinus tract leading from the kidney and opening in the loin permitted a continuous discharge of purulent urine.

Cutaneous urinary fistulas also arise as the result of spontaneous rupture of a hydronephrotic kidney. Coupland and Lawton<sup>64</sup> treated a patient with a bifid ureter which was obstructed at the vesical orifice by a large irregular stone; the subsequent urinary stasis caused a pres-

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54. Vright, cited by Weiser.<sup>30</sup>

55. Broca, C. D., cited by Chazet.<sup>15</sup>

56. Lucas, cited by Weiser.<sup>30</sup>

57. Doyen, T. B., cited by Chazet.<sup>15</sup>

58. McClelland, cited by Morris.<sup>3</sup>

59. Weeks, S. H., cited by Morris.<sup>3</sup>

60. Gaston, J. M., cited by Morris.<sup>3</sup>

61. Whately, F.: Renal Calculus Which was Discharged Through a Fistulous Opening in the Loin, *Tr. Path. Soc. London* 26:128, 1874-1875.

62. Crabtree, E. G.: Calculous Pyonephrosis with Subdiaphragmatic Abscess, *Boston M. & S. J.* 196:825, 1927.

63. La Peyre, cited by Morris.<sup>3</sup>

64. Coupland and Lawton, cited by Morris.<sup>3</sup>

sure atrophy with rupture of the renal cortex, and the extravasated urine finally perforated the lumbar muscles. Morris described a similar case, in which the obstruction was due to a ureteral stone.

#### URETERAL FISTULA

Spontaneous perforation of the ureters is much less common than perforation of the kidney. However, the same pathologic conditions that produce renal fistula are responsible for the great majority of ureteral sinuses.

*Uretero-Intestinal Fistula.*—The anatomic relationship of the left ureter and the stomach precludes the formation of a gastro-ureteral fistula unless some anomalous condition is present.

Communications between the right ureter and the duodenum have occurred but are rare. Several questionable cases have been reported, but careful study shows that most of them were those of nephro-duodenal fistulas. Davis<sup>65</sup> cited the only authentic case of uretero-duodenal fistula. The patient was 29 years of age, and complained of a dull, aching pain in the left flank associated with fever, chills, pyuria, frequency and burning on urination. A pyelogram revealed the extravasation of the injected medium from the upper end of the ureter into the periureteral tissue. At operation, a sinus tract was found uniting the ureter and the duodenum. The opening in the duodenum was closed, and the kidney was removed. The patient made a good recovery. There was sudden cessation of all urinary symptoms following the operation. The kidney was examined microscopically, and no evidence of tuberculosis could be found. Davis believed that the non-specific perirenal abscess ruptured into the ureter and also emptied into the duodenum, thus forming the artificial communication.

Stones may ulcerate through the ureteral wall and form a peri-ureteral abscess which may empty into the colon. Greene<sup>66</sup> observed a patient in whom dysuria and frequency of urination were outstanding symptoms. Pyelographic studies disclosed a distorted renal pelvis, and at the level of the fourth lumbar vertebra the urographic solution was seen to escape from the ureter and enter the cecum and ascending colon. Operative findings substantiated the diagnosis of ureterocolic fistula. Wells<sup>67</sup> cited the case of a patient who passed urinary calculi in the feces. He concluded that the stones ulcerated through the lower

65. Davis, E. G.: Duodeno-Ureteral Fistula of Spontaneous Origin, J. A. M. A. **70**:376 (Feb. 9) 1918.

66. Greene, L. B.: Uretero-Colonic Fistula, Ann. Surg. **86**:130, 1927.

67. Wells, S.: Urinary Calculus Discharged Through the Rectum, Tr. Path. Soc. London **5**:202, 1854.

ureter, formed a periprostatic and perirectal abscess which ruptured into the rectum, thus permitting urine and stones to escape with the stools.

Retrocecal appendix may cause a perityphlic abscess which may burrow its way into the ureter and empty its purulent contents by means of the urinary tract. LeCompte emphasized that such abscesses not only communicate with the ureter, cecum and colon but may open externally by penetrating the lumbar muscles, thus producing a urinary-iliocolostomy. Chrzeltzer<sup>68</sup> also found an appendico-ureteral fistula due to an old appendical abscess.

Most ureterocolic fistulas result from tuberculous infections. Doering<sup>69</sup> treated a patient who had a cold abscess which arose from a tuberculous hip and eroded into the ureter, producing pyuria, and then ruptured the colon. Casper,<sup>70</sup> Newman<sup>71</sup> and Doering each encountered uretero-intestinal fistulas resulting from tuberculous periureteritis. Van Vranken<sup>72</sup> observed a patient with a swelling in the groin just above Poupart's ligament. He incised the abscess and found that it communicated with the colon. Feces drained from the opening for about one month, and then urine could be detected in the discharge. Evidently the psoas abscess had perforated both the colon and the ureter, forming a ureterocolostomy.

*Uretero-Abdominal Fistula.*—One of the most unusual forms of ureteral fistula is that in which there is a communication with the peritoneal cavity.

Dystrophies of the ureter, whether congenital or acquired, are conducive to rupture of the ureteral lumen. Foster, Pflaum and Sugoi<sup>73</sup> described the case of a child 14 days old who died of urinary ascites. Autopsy showed atresia of the right ureter with an aplastic right kidney. The left ureter had a normal lumen, but just proximal to its vesical orifice the ureter was kinked, producing complete obstruction. The ureter was dilated and tortuous, and was the seat of an advanced ureteritis. Just above the obstruction was a small perforation of the ureteral wall which permitted the escape of urine into the peritoneal cavity.

68. Chrzeltzer: Beitrag zur Hämaturie nach Appendizitis, Ztschr. f. Urol. **16**:408, 1922.

69. Doering, cited by Weiser.<sup>30</sup>

70. Casper, L.: Ureteral Fistula and Ureteral Suppurations, Ztschr. f. Urol. **18**:545, 1924.

71. Newman, cited by Weiser.<sup>30</sup>

72. Van Vranken, A. T.: Uretero-Intestinal Fistula as Result of Abdominal Abscess not Due to Appendicitis, with Recovery, Tr. New York M. A. **11**:553, 1894.

73. Foster, Pflaum and Sugoi, cited by Weiser.<sup>30</sup>

Tuberculous ureteritis with its inflammatory necrosis may perforate the ureter and empty its purulent contents into the abdominal cavity, producing the clinical picture of peritonitis. Mitterstiller<sup>74</sup> performed a laparotomy for chronic peritonitis, on a woman, 28 years of age, and found multiple intraperitoneal and extraperitoneal abscesses caused by the tuberculous ulceration of the ureter at the level where it crossed the iliac vessels. The findings were corroborated at necropsy.

In case 5 of our series the ureterovesicoperitoneal fistula was due to an extensive tuberculous necrosis of the bladder and ureter. The urine secreted by the left kidney entered the peritoneal cavity either by the ureteroperitoneal or by the vesicoperitoneal fistula, and then escaped from the abdominal cavity by means of an old lumbar sinus.

A calculus may partially or completely obstruct the ureter, causing not only a hydro-ureter but also ureteritis, both of which weaken the walls of the ureter and may cause a perforation. Dupuytren<sup>75</sup> observed the case of a young woman with a left lumbar abscess, which was incised and drained. Subsequently, signs of chronic peritonitis developed, and the patient died. At autopsy, it was found that a stone had eroded through the musculature of the ureter and permitted the infected urine to seep out into the peritoneal cavity.

As these histories indicate, most cases of urinary ascites terminate fatally owing to peritonitis precipitated by the contaminated urine.

*Ureteroperiureteral Fistula.*—Stones may ulcerate their way through the walls of the ureter producing a periureteral abscess which drains into the ureteral lumen, causing pyuria. Frenkel<sup>76</sup> gathered the records of eleven cases of this type. Berry<sup>77</sup> encountered a phlegmonous involvement of the periureteral tissue due to urinary extravasation and found that a small stone had perforated the ureter. Schmidt<sup>78</sup> treated a patient with periureteritis which was secondary to perforation of the ureteral wall by a stone. The patient had symptoms suggesting carcinoma of the cervix, and only after careful study was it found that the extensive periureteritis was due to urinary extravasation.

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74. Mitterstiller, S.: Ueber einem Fall von Entleerung einer Pyonephrose in die Peritonealhohle, *Ztschr. f. Urol.* **14**:168, 1920.

75. Dupuytren, cited by Morris.<sup>3</sup>

76. Frenkel, cited by Weiser.<sup>30</sup>

77. Berry, J.: Perforation of Ureter by Calculus: Extravasation of Urine, *Brit. J. Surg.* **8**:372, 1921.

78. Schmidt, H. H.: Perforation of Ureter by Calculous Invisible Roentgenographically and Causing Symptoms Resembling Cancer Uterus, *Zentralbl. f. Gynäk.* **54**:274, 1930.

Diverticula of the ureter, which usually represent congenital dystrophy, may rupture spontaneously. Stevens<sup>79</sup> observed the case of a man, 59 years of age, who complained of fever and chills and pain in the left lower flank; urinary symptoms were entirely absent.

Cystoscopic and pyelographic examination revealed a small diverticulum at the ureteropelvic junction; the diverticulum had perforated and was draining a coexisting perinephritic abscess.

Perinephritic abscesses resulting from osteomyelitis or infections of the adjacent soft tissues may rupture into the ureter and cause a fistula. Lindsjö<sup>80</sup> cited the case of a patient who suffered for eighteen months from intermittent pyuria and pains in the left hip. A specimen of urine collected from the left ureter was loaded with pus. At operation a large psoas abscess was found which had arisen from a chronic osteomyelitis of the hip bone. The abscess had penetrated the walls of the ureter and was emptying its purulent contents into the urinary stream.

Tuberculous ureteritis with perforation and formation of periureteral abscesses may closely simulate some intra-abdominal lesions. Rathbun<sup>81</sup> encountered a scrofulous periureteral abscess which communicated with the left ureter in a patient in whom the referring physician had suspected an extra-uterine pregnancy.

Our case (case 4) of ureteroperiureteral fistula illustrates the complications that may follow a perinephritic abscess. The kidney was the seat of cortical abscesses; the infection spread to the perinephrium, extending down the course of the ureter and forming a periureteral abscess which ruptured into the ureter, causing cystitis with pyuria.

*Uterovesical Fistula.*—Abnormal spontaneous communications between the ureter and bladder are unusual. Occasionally a ureteral stone may be arrested at the vesical orifice, ulcerate its way through the walls of the ureter and form a periureteral abscess which may penetrate the bladder. Occasionally a pelvic abscess secondary to acute salpingitis ruptures into both the ureter and the bladder, forming a uterovesical fistula, such as Ottow<sup>82</sup> described. Schottelius<sup>83</sup> treated two patients suffering from periureteritis. The inflammation had spread

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79. Stevens, A. R.: Diverticulum of Ureter: Acute Inflammation and Spontaneous Perforation, *J. Urol.* **16**:157, 1926.

80. Lindsjö: Case of Pyuria with Unusual Etiology, *Acta pædiat.* **4**:104, 1925.

81. Rathbun, N. P.: Necrosis of the Ureter, Perforation, Peri-Ureteral Abscess, *J. Urol.* **17**:329, 1927.

82. Ottow, B.: Rupture of Abscess of Internal Genitalia into Bladder and Ureter, *Zentralbl. f. Gynäk.* **53**:2551, 1929.

83. Schottelius, M.: Zwei Fälle von einseitiger Hydronephrose (Uterovesicalfistel), *Virchows Arch. f. path. Anat.* **71**:268, 1877.

to the ureters, producing ureteritis and hydro-ureter. The diseased ureteral walls ruptured, permitting urine to escape into the periureteral tissue. The resulting abscess opened into the bladder and formed a uretrovesical fistula.

*Ureterovaginal Fistula.*—Fistulous tracts joining the vagina and the ureters as the result of local disease are very interesting: Weinzierl<sup>84</sup> referred to a case in which a fistula arose from the prolonged use of a pessary. The constant irritation of the pessary with its inflammatory reaction and pressure necrosis produced localized abscesses which opened both into the vagina and into the ureter, permitting urine to escape through the vulva. Morris treated a young girl for renal tuberculosis and cystitis. The bladder symptoms became so pronounced that the patient dribbled urine constantly. On careful examination, an advanced tuberculous ureteritis with a cold abscess was found. The inflammatory process had extended to the periureteral tissues and finally had eroded its way into the vagina. All the urine excreted by the isolateral kidney escaped by this fistulous tract. Jurgen<sup>85</sup> and Kretchmer<sup>86</sup> each described a case of ureterovaginal fistula arising from irradiation necrosis following the application of radium for carcinoma of the cervix.

An interesting case was described by Konwer<sup>87</sup> and Schwartz<sup>88</sup> in which a stone had ulcerated its way through the coats of the ureter and had formed a periureteral abscess which had perforated the walls of the vagina.

#### DIAGNOSIS

In the majority of the cases cited, the diagnosis was made from the history and the findings at operation or autopsy. At the present time, cystoscopic and roentgenographic studies make the diagnosis of urinary fistula relatively easy, and there is no reason why a preoperative diagnosis of all such fistulas should not be made.

#### TREATMENT

The best treatment for spontaneous urinary fistula is prophylaxis. The infrequent occurrence of this condition at the present time signifies that, in general, renal diseases are not allowed to progress to the stage at which fistulas are formed. Tuberculous kidneys usually are removed before they reach the point of pronounced caseous degeneration; stones are extracted before they penetrate the walls of the pelvis or ureter;

84. Weinzierl, cited by Weiser.<sup>30</sup>

85. Jurgen, O., cited by Weiser.<sup>30</sup>

86. Kretchmer, cited by Weiser.<sup>30</sup>

87. Konwer, cited by Weiser.<sup>30</sup>



perinephritic abscesses are drained before they ulcerate into the kidney, and hydronephrotic kidneys are prevented from rupturing by early removal of the ureteral obstruction and the establishment of free drainage. If urinary fistulas develop, it usually means that the patient has refused medical attention until the disease process is well established.

The therapeutic measures employed in the treatment of spontaneous renal fistulas are governed by the general condition of the patient, the functional status of the kidneys, the type of disease present and the organs or tissues involved. Attempts to secure a primary closure of the sinus tract usually are unsuccessful unless the causative factors are removed. As such cases represent advanced renal tuberculosis, nephrolithiasis, pyonephrosis or hydronephrosis with atrophy of the parenchymal tissue, it is generally necessary to sacrifice the kidney.

Many patients of this type represent such bad surgical risks that a primary nephrectomy is contraindicated; however, an incision and drainage of the coexisting perirenal abscess usually improves the general condition so that the kidney may be removed at a later date with much less danger. In our case (case 2) of nephrocolic fistula such a conservative procedure was followed, and in spite of three operations the patient made a satisfactory recovery. At times the chronic infection associated with most renal fistulas has so reduced the vitality of the patient that even the most conservative surgical procedure is of no avail.

If the fistula communicates with a hollow viscus, such as the gastrointestinal tract, the opening in the cavity is closed and the kidney is removed. Very few fistulas persist after the kidney has been excised, unless the initial disease has become firmly established in the perirenal tissues.

The treatment of ureteral fistulas is usually more conservative, depending entirely on the condition of the isolateral kidney. If a small stone has perforated the ureter, incision and drainage of the periureteral abscess and the use of indwelling ureteral catheters sometimes result in cure. If pyonephrosis has developed secondary to ureteral obstruction, the kidney usually must be sacrificed. In our case of ureteral-periureteral fistula, which was secondary to pyonephrosis associated with a perirenal abscess which had ruptured into the ureter, the removal of the kidney was necessary in order to close the fistula. In most patients with renal or ureteral fistulas, the condition constitutes a complication arising from advanced kidney disease and is attended with a high rate of mortality. The infected urine infiltrates all the surrounding tissues and organs, producing chemical and bacterial irritations which are expressed by severe febrile and septic reactions. In our series of four patients who were subjected to operation, one death occurred.

## SUMMARY

This report includes the detailed study of three types of spontaneous renal fistulas; nephrocolic, nephroperirenal and renochylous fistula, and one case each of spontaneous ureterovesicoperitoneal and ureteroperi-ureteral fistula.

Spontaneous renal and ureteral fistulas are the result of advanced kidney disease, such as tuberculosis, nephrolithiasis, pyonephrosis, hydronephrosis or neoplastic disease, and occasionally arise from a perinephritic abscess that is secondary to caries of the vertebrae, perityphilitic abscess, pelvic disease or peripheral infections, such as boils.

The diagnosis is made on the basis of the clinical symptoms, corroborated by cystoscopic and roentgenographic studies.

The most important consideration in the treatment of spontaneous urinary fistulas is prophylaxis, the prevention of advanced kidney diseases to the stage of fistula formation by the use of early corrective measures. Closure of a renal fistula usually requires nephrectomy, as the kidney is so generally diseased that practically no functioning tissue remains. In the case of patients who constitute a grave surgical risk, conservative measures are indicated; primary drainage of a perinephritic abscess usually results in improvement, so that a nephrectomy may be performed later. The use of indwelling ureteral catheters may facilitate the repair of a ureteral fistula, but usually the kidney is harboring infection which has destroyed the parenchyma to such an extent that its conservation is useless.

# EFFECT OF COMPLETE AND PARTIAL STARVATION ON THE RATE OF FIBROPLASIA IN THE HEALING WOUND

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The effect of complete and partial starvation on the healing of wounds is of fundamental importance to the surgeon. Malnourished patients must occasionally be subjected to surgical procedures, and often it is necessary to restrict the amount of diet after operation. Only too frequently we observe the wounds of undernourished patients, particularly those of children, healing slowly and becoming infected.<sup>1</sup> Unfortunately, in the clinic, however, it is not always possible to establish the exact nature of a malnutrition or to determine the deficiency of the previous diet which produced it. So, too, it is quite impossible to tell whether a prolonged healing time of a wound is the result of malnutrition alone or of other causes more obscure. To interpret adequately the relation of diet to the healing wound, one must have carefully collected data on experimental animals—data which give the preoperative state of nutrition and the dietary regimen as well as the postoperative state.

Repeated experiments have shown that starvation actually accelerates the rate of cellular division. Morgan,<sup>2</sup> for example, found that the legs of salamanders regenerated as rapidly when the animals were starved as when they were well nourished. Gaglio,<sup>3</sup> studying the problem histologically, found mitotic figures more frequent in the

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1. Harvey, Samuel C.: Post-Operative Complications, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1927, vol. 1, p. 552.

2. Morgan, Thomas H.: The Physiology of Regeneration, *J. Exper. Zool.* 3:457, 1906.

3. Gaglio, G.: Sulla alterazioni istologiche e funzionali dei muscoli durante l'inanizione, *Arch. di sc. med.* 7:301, 1884; cited by Morgulis.

tissues of starved frogs than in normal frogs, while Morpurgo<sup>4</sup> saw a similar increase in cells of pigeons. Morgulis,<sup>5</sup> following a careful study of the entire problem, came to believe that a reduction in cell cytoplasm occurred, with but little reduction in the size of the nucleus. This disturbed nuclear cytoplasmic ratio, he believed, resulted in an increased rate of cell division in an effort to restore the proper balance. Theoretically, then, starvation should not delay healing of the wound, but actually, as has been mentioned, there are disturbing factors in association with complete or partial starvation which cause the wounds to show not an acceleration in healing, but rather a slower rate of repair. Consequently, it is not surprising that it is a common belief that complete or partial starvation delays the healing of the wound, and this may be true because regeneration is only one phase of the healing.

It is the object of our investigation, therefore, to dissociate starvation and partial starvation (reduction in the amount of an adequate diet) from other types of malnutrition and to study their effects on the healing wound. To a certain extent, the strength of the wound has been found to be directly proportional to the degree of healing attained, and, therefore, strength will be adopted here as the criterion for testing the rate of repair. In order to determine the relation between age and these two dietary changes, it will be necessary to make two studies, using, on the one hand, adult animals and, on the other, young ones.

#### METHOD

The rat was particularly good for our purposes because of its relatively high degree of immunity to infection, as well as to the large amount of work that has been done on its metabolism.

Because we found that age made such a difference in the rate of healing,<sup>6</sup> young and old rats of definite specifications were selected. The adults employed averaged 194 Gm. in weight and were at least 5 months old. They were kept in individual cages. The quantity of the adequate diet given to the controls was determined by the amount of the same diet consumed by a normal group of rats in a previous experiment (tables 1 and 2). This was on the average 3.4 per cent of the body weight daily. The partially starved rats were given one-half this amount, or 1.7 per cent daily, and those completely starved were given only water. In order

4. Morpurgo, B.: Sull processo fisiologico di neoformazione cellulare durante la inanizione acuto dell' organismo, *Arch. di sc. med.* **12**:395, 1888; cited by Morgulis.

5. (a) Morgulis, S.; Howes, P. E., and Hawk, P. B.: Studies on Tissues of Fasting Animals, *Biol. Bull.* **28**:397, 1915. (b) Morgulis, S.: Fasting and Under-nutrition: A Biological and Sociological Study of Inanition, New York, F. P. Dutton & Co., 1923.

6. Howes, E. L., and Harvey, S. C.: The Age Factor in the Velocity of the Growth of Fibroblasts in the Healing Wound, *J. Exper. Med.* **55**:577 (April 1) 1932.

to establish definitely the malnutrition before the wound was inflicted, the partially starved animals were placed on the diet one week before operation, but those completely starved were for obvious reasons not placed on their water diet until the day before operation.

The young rats selected were under 2 months of age and weighed 78 Gm. on the average. The controls of this group were given a normal dietary intake of 13 per cent of the body weight daily (table 2), and consequently those partially starved received 6.5 per cent daily. Again, those completely starved were given only water. It will be noted that these young rats were given four times the quantity of the ration allowed the adults, but both groups received equivalent amounts in proportion to their requirements. Young rats need four times as much

TABLE 1.—*Standard Balanced Diet (Smith and Moise)*

Percentage Composition		Calories per Kg. of Food	Apportionment of Total Calories, per Cent	
Casein.....	18	738	Protein.....	13.8
Starch.....	51	2,091	Carbohydrate.....	39.2
Crisco.....	22	2,046	Fat.....	47.0
Cod liver oil.....	5	465		
Salts (Osborne and Mendel mixture).....	4			
		5,340		
Lettuce twice a week 70 mg. of yeast daily				

TABLE 2.—*Consumption of Food and Variation in Weight of Young and Adult Rats on the Standard Diet\**

	Adult Rats		Young Rats	
	Start to Operation	Operation to Death	Start to Operation	Operation to Death
Difference in weight per day, per cent.....	+0.26	—0.45	+4.1	+3.1
Food consumed per day, per cent.....	4.3	2.5	12.0	11.0
	Av. 3.4		Av. 11.5	
Protein consumed per day, per cent.....	0.75	0.45	2.2	2.0
Calories of food consumed per day, per cent...	23.0	13.0	59.0	55.0
Calories of protein consumed per day, per cent	3.1	1.7	8.1	7.5

\* The calculations are based on the percentage of body weight at the start of the experiment. The data are compiled after Towes and Harvey.<sup>6</sup>

food as adults (table 2). The weights of both the adult and the young rats completely starved were recorded daily, while those only partially starved were weighed every third day.

The details of wounding the stomachs and of testing the healing strengths at regular intervals have been given elsewhere.<sup>7</sup> Essentially, it consisted in making a wound 1 cm. in length through the wall of the cardiac or rumen portion of the stomach. This was subsequently sutured in two layers with no. 000 plain catgut, approximating first the squamous cell layer and then the muscularis and serosa. After the animal was killed at the given postoperative interval, the strength of the wound was determined by finding the amount of air pressure necessary to rupture it. The machine developed for these observations was the same as that used in former studies.<sup>8</sup>

7. Harvey, S. C., and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound, *Ann. Surg.* **91**:641 (May) 1930.

8. (a) Harvey, S. C.: The Velocity of the Growth of Fibroblasts in the Healing Wound, *Arch. Surg.* **18**:1227 (April) 1929. (b) Harvey and Howes.<sup>7</sup>

Postmortem studies were made not only of the wound but of the organs of the body. Microscopic sections were prepared where deemed necessary.

In the previous investigations it was found that the curve of strength of the wounds plotted at daily intervals showed three distinct phases of healing (chart 1). The first phase was marked by a latent period of four days during which the wound had only the strength imparted to it by the sutures and the deposited fibrin. During the second phase, from the fourth to the tenth day, fibroplasia developed and strength increased rapidly. In the third or final phase, from the tenth to the fourteenth days, some of the wounds became stronger than the surrounding tissues, and consequently, the points of rupture were elsewhere than in the wound. On the final day of this third phase, all of the wounds became stronger, and, therefore, this day was considered the end-point. Because we found that the presence of the sutures caused variability in the strength determinations during the first phase, in this experiment we did not seek the readings over this interval. Likewise, we omitted

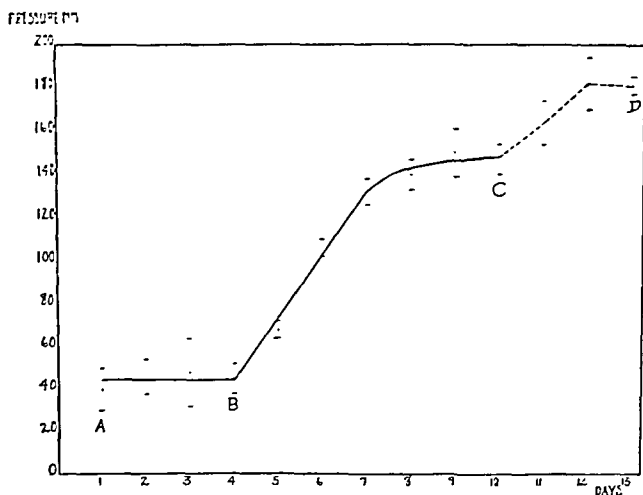


Chart 1.—Typical healing curve for wound of the stomach: A to B, period of fibrinous healing; B to C, period of fibrous healing, ruptures in the wounds; C to D, continuation of fibrous healing, ruptures in the wounds and elsewhere in the wall of the stomach.

the final period for many readings were obtained in this phase which gave the strength of the wall of the stomach and not that of the wound. It was deemed highly important, however, to note the day on which rupture of the stomach other than at the site of the wound began to occur. As a result, our determinations concern themselves only with the phase of fibroplasia. In order to reduce individual biologic variations undoubtedly existent, the strengths of five different wounds in the stomach were averaged for each twenty-four hour postoperative interval from the fifth to the tenth days, inclusive. With these averages, curves were constructed in the manner previously described.<sup>5a</sup>

#### RESULTS AND COMPARISON OF THE CURVES

*Adult Rats.*—A. Completely Starved Group (table 3): The adult rats withstood complete starvation until the tenth day; one died on the eighth day, two on the ninth and four on the tenth. The one remaining alive on the tenth day was extremely weak and lethargic.

The curve for healing strength of their wounds was somewhat different than those for the other adult rats (chart 2). All the curves were practically the same until the fifth day, but on the following two days the rate of ascent of the curve for starvation fell below the other two curves. This decrease in the rate was of short duration, however, for on the eighth and ninth days of healing, the curve again mounted more rapidly and the strengths registered were greater than those of the rats receiving the half caloric diet and the full diet. During the entire nine days of starvation, the final phase of the curve for healing strength was not reached, but then this period was not gained in the

TABLE 3.—*Average Strengths of Stomach Wounds for Adult Rats\**

Post-operative Days	On Standard Diet		With Starvation		With Partial Starvation	
	Mm. of Mercury	Standard Deviation of the Mean	Mm. of Mercury	Standard Deviation of the Mean	Mm. of Mercury	Standard Deviation of the Mean
5	71.0	± 5.0	72.0	± 6.0	69.0	± 7.0
6	107.0	± 6.0	93.0	± 6.0	96.0	± 6.4
7	135.0	± 5.0	133.0	± 11.0	106.0	± 6.0
8	143.0	± 6.8	161.0	± 10.0	147.0	± 9.0
9	153.0	± 10.0	171.0	± 8.0	154.0	± 6.0
10	150.5	± 7.0	Death		155.0	± 10.0
	Final period				Final period	

\* All of the breaks occurred in the wounds.

TABLE 4.—*Percentage Loss in Body Weight of the Adult Starved Group*

Postoperative Days	Percentage	Postoperative Days	Percentage
1.....	7.8	6.....	6.9
2.....	6.2	7.....	4.5
3.....	5.6	8.....	4.0
4.....	5.7	9.....	3.0
5.....	5.7	10.....	2.8

curve representative of the full diet until the tenth day. It can be concluded, therefore, that although this curve for starvation was somewhat different in form than the curve for the controls, yet in general the rate of healing of these wounds was not markedly changed from the normal rate.

Determinations of the losses in weight of these rats calculated from the weight at the onset of the study showed that the average percentage loss of body weight was more rapid during the first day (7 per cent), and that the amount lost decreased daily as starvation progressed (table 4). These rats drank only a minimum amount of water. At autopsy, the incidence of wound infection in this group was but 2 per cent, or identical with that found in the controls. The postmortem observations substantiated the observations on loss of weight, for in every case body fat was either entirely absent from the usual depots

or so reduced in amounts as to be found with difficulty. All skeletal muscles were in an advanced state of atrophy, and practically every stomach contained a large hair ball.

B. Partially Starved Group: The curve of healing in these animals did not differ markedly from the curve for the controls, except for some slowing of the rate on the sixth and seventh day (table 3 and chart 2). The average daily loss in body weight was appreciably less than in the completely starved group, being here but 3 per cent or about

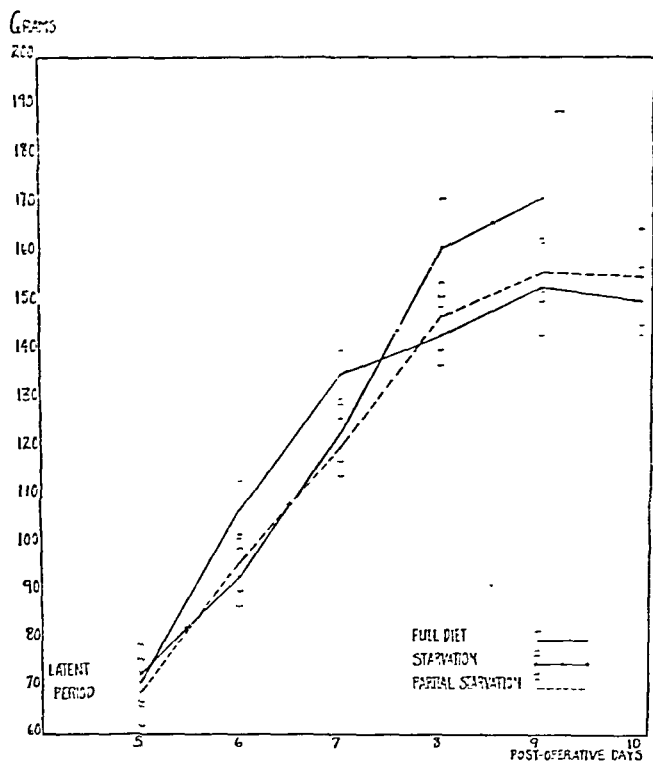


Chart 2.—Strength of stomach wounds for adult rats. Note the greater rate of healing on the seventh to the eighth days in the curve for starvation.

half that observed on complete starvation. The incidence of infection was, however, higher than that found with starvation, 8 per cent being found in the abdominal wounds and 3 per cent in the peritoneal cavities. At autopsy, more fat was observed in the depots, and there was decidedly less muscular atrophy than had been found in the completely starved animals. Taking the progress of healing in its entirety, partial starvation did not retard the rate of the healing of the wounds in these adult rats.

*Young Rats.*—A. Completely Starved Group (table 5): The young rats did not withstand complete starvation long enough for their wounds



to give satisfactory determinations of healing strength. None of the animals lived longer than the fifth day postoperatively, and the majority died on the fourth day. Wounds tested in two surviving animals on

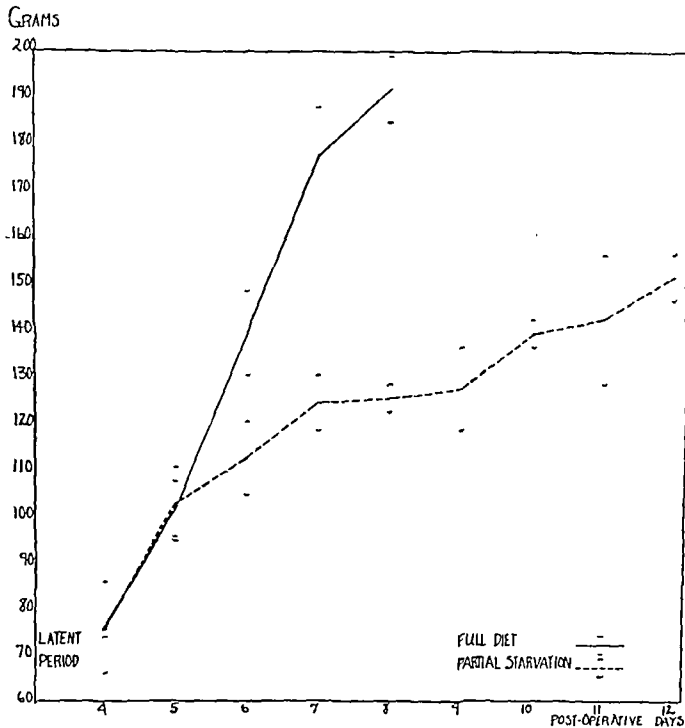


Chart 3.—Strength of stomach wounds for young rats.

TABLE 5.—Average Strengths of Stomach Wounds for Young Rats\*

Post-operative Days	On Standard Diet		With Starvation		With Partial Starvation	
	Mm. of Mercury	Standard Deviation of the Mean	Mm. of Mercury	Standard Deviation of the Mean	Mm. of Mercury	Standard Deviation of the Mean
4	76.0	± 2.0	78.0	± 3.0	76.6	± 9.5
5	102.0	± 6.0	Death		103.7	± 8.0
6	140.0	± 9.0	.....		113.2	± 8.0
7	178.0	±10.0	.....		125.6	± 6.7
8	192.0	± 7.0	.....		126.0	± 3.7
9	Final period		.....		128.3	± 9.0
10	.....		.....		140.5	± 3.7
11	.....		.....		143.2	±14.0
12	.....		.....		152.0	± 5.7

\* All of the breaks occurred in the wounds.

the fourth day had only the strength given to them by the sutures and fibrinous deposits. There was no evidence of fibroplasia microscopically.

B. Partially Starved Group: The plotted determinations of the healing strength of the wounds for this group had the same general trend as the controls until the fifth day (table 5, chart 3). After this

day, however, the rate of repair fell off rapidly, and the increase in strength of the wounds from day to day was so small that the curve tended to flatten out. Healing was so retarded that the entrance of the curve into its final period was not reached during thirteen days of testing. In the last few days the strength even fell below that for the adult control. This was an astounding result for the rate of fibroplasia in young rats has always been found to be greater than in adult rats.<sup>6</sup>

Unlike the adults who had shown but little desire to move about, these young animals were very active. In fact, at times it seemed as though they were in a state of tetany. The slightest noise would cause them to jump to the tops or sides of their cages. They also drank more water than the controls, and despite an average daily loss in body weight of 1.9 per cent, they continued to grow in body length (table 6). The incidence of wound infection was 5 per cent both in the abdominal wall and in the peritoneal cavity.

TABLE 6.—*Weight Data for Young Rats Partially Starved*

	Initial Body Weight, Gm.	Final, Gm.	Per Cent Lost Daily	Daily per Cent Weight Lost
Four days.....	76	71	6.6	1.6
Five days.....	76	66	13.2	2.6
Six days.....	71	60	15.5	2.6
Seven days.....	77	65	15.6	2.2
Eight days.....	55	45	18.2	2.2
Nine days.....	86	71	17.4	1.9
Ten days.....	71	57	19.7	1.9
Eleven days.....	86	66	23.3	2.1
Twelve days.....	78	71	9.0	0.8
Average daily per cent weight lost.....				1.9

## COMMENT

The comparison of the curves for the wounds of the adult rats indicates that the rates of fibroplasia were practically the same under all three dietary conditions. This proximity of the three curves demonstrates that an acute state of malnutrition can exist in adult rats without appreciably affecting the rate of repair of soft tissue. It is highly probable that the explanation of this ability of the wound to heal in spite of caloric deficiencies of the diet lies in the compensating mechanisms of metabolism known to occur in association with inanition.<sup>9</sup> The time required for exhaustion of the various essential food elements during complete or partial starvation depends on (1) the amounts of these substances consumed in the diet, (2) the amounts available within the body as stored reserves and (3) the rapidity with which they

9. Benedict, F. G.: A Study of Prolonged Fasting. Washington, D. C., Carnegie Institute, bull. no. 203, 1915. Jackson, C. M.: The Effects of Inanition and Malnutrition upon Growth and Structure, Philadelphia. P. Blakiston's Son & Co., 1925.

are consumed. The exact character of the effect of complete or partial inanition, then, is exceedingly variable in a group of animals. Exhaustion of all essential food elements at the same time is absolutely impossible. It is recognized that for a varying period of time the nutrient level of the blood is maintained by the mobilization of foodstuffs from the reserve depots. The glycogen of the liver is said to be utilized first; secondly, the depot fat, and lastly, the proteins in the tissues. The extent of metabolic adjustment is dependent in part on the caloric insufficiency of the diet; consequently less metabolic adjustment was necessary in the partially starved rats and there was found less depletion of body fat and no atrophy of the muscles. This was borne out by the losses in weight, for the greater losses were in the completely starved rats.

The irregularity of the rate of ascent of the curve for starvation in the adult rats suggests that a multiplicity of factors affected it. The selection of the animals with their variations in their original food reserves might offer a possible explanation for this irregularity. But even if this selection were given all the credit due to it for maintaining the rate of repair, the important conclusion cannot be escaped that in general the rate of healing in adults was not decreased by starvation. This point is particularly well emphasized by the degree of healing strength attained by the wounds of the animals in extreme starvation on the eight and ninth day.

Studies on protein metabolism during starvation have shown that in the first two days of complete fasting the excretory products of nitrogen increase, but subsequently they establish themselves at a constant level. In the final days of starvation, the metabolism is almost all if not entirely protein, for there is again a definite increase in the rate of tissue destruction, and during this period, therefore, there would be an increase in the available amounts of amino-acids. It is more than pure theory, then, when we assume that the increased rate of healing during the final days of starvation was caused by this accelerated metabolism of proteins. To substantiate this there is the work of Carrel and Baker,<sup>10</sup> who have shown that in tissue cultures proteins are the necessary stimulants for cell proliferation, and Clark<sup>11</sup> and Harvey and Howes<sup>7</sup> have demonstrated that an increased quantity of proteins in the diet stimulates the rate of healing of the wound.

Another possible explanation for the terminal increase in the rate of healing of the wounds in the completely starved adult rats may lie in the changes in the acid-base equilibrium known to occur during the

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10. Carrel, A., and Baker, L. E.: The Chemical Nature of Substances Required for Cell Multiplication, *J. Exper. Med.* **44**:503, 1926.

11. Clark, A. H.: The Effect of Diet on the Healing of Wounds, *Bull. Johns Hopkins Hosp.* **30**:117, 1919.

concluding days of starvation. Although true acidosis has never been satisfactorily demonstrated in rats, the starvation they underwent undoubtedly reduced their alkaline reserve, and if such is the case, it would seem that the findings of Herrmannsdorfer<sup>12</sup> would explain the increased rate of repair. Herrmannsdorfer found that if an alkaline diet was given to patients with wounds, healing was delayed, while the reverse was true with an acid diet and when there was partial acidosis.

In addition, the disturbed nuclear ratio must not be forgotten as a possible factor stimulating healing of the wound during these terminal days of starvation. We have mentioned before the theory that starvation increases the rate of cellular division by decreasing the nuclear-cytoplasmic ratio. Cells in which this change has taken place approach an embryonic state wherein the cytoplasm is quantitatively reduced while the nuclei remain unchanged. The result is an accentuation of mitosis in an effort to restore the ratio.

Exactly which of these factors controlled the increased rate of healing in the last two days of starvation, we do not know. It is evident, however, that the increased rate during the final two days was caused by some disturbed mechanism produced by complete starvation, for it did not occur with partial starvation. Perhaps, though, we are giving too much credit to the rôle of the general metabolism in the healing of wounds. We have not forgotten the importance of local conditions in the healing wounds, but wish only to emphasize the influence of the general metabolism. This point of view is supported by the works of Clark<sup>11</sup> and Herrmannsdorfer.<sup>12</sup>

Some may consider that the stomachs of the completely starved rats were more at rest than those of the partially starved rats, and that thus an inhibiting factor was removed allowing cells of less proliferative power to heal at a normal rate. That cells do not have less but actually more proliferative power during starvation we have already mentioned. Besides, Howes<sup>13</sup> has shown that it is not so much freedom from function that aids healing as freedom from irritation. In the stomachs of these completely starved rats we found hair balls, and it has already been postulated by Pappenheimer and co-workers<sup>14</sup> that

12. Herrmannsdorfer, A.: Ueber den Einfluss der Nahrung auf die Pufferkapazität des Blutes und den Heilverlauf und Keimgehalt granulierender Wunden. *Deutsche Ztschr. f. Chir.* **200**:534, 1927.

13. Howes, E. L.: Der Einfluss der Nahrung auf den Heilungsablauf von Magenwunden. *Beitr. z. path. Anat. u. z. allg. Path.* **88**:435, 1932.

14. Pappenheimer, Alwin M., and Larimore, Louise D.: The Occurrence of Gastric Lesions in Rats: Their Relation to Dietary Deficiency and Hair Ingestion, *J. Exper. Med.* **40**:719 (Dec. 1) 1924.

hair in the stomach produces sufficient irritation to cause ulcerative lesions, providing there is some deficiency of the diet. Yet the presence of these hair balls with their possible irritation and distention of the stomachs did not retard healing. The difference in the amount of rest, then, did not allow cells of less proliferative power to heal at a normal rate. It is true that rest is of great importance in wound healing in general, but one which we are inclined to discount to a large extent as an influencing factor in this study.

The fact that the different diets did not influence the rate of healing emphasizes the great range in the amount of food in the stomach over which wounds in this organ will heal. While on the one extreme healing was not appreciably changed by starvation, yet on the other it was not impeded by the digestion of a full diet. Clinically, this has been known for some time. In America it is the practice in gastric cases to reduce the diet markedly postoperatively over a longer period of time than in most European clinics. In France and Germany the ration is more liberal, and the patients are returned to their normal diet much more quickly than they are in this country. Both methods can be used because of this ability of the wounds of the stomach to heal under great variations in the amount of food contained. Of course, the postoperative dietary regimen would be most ideal if it would maintain the nutritional state of the patient at an optimum. However, the one drawback to a rapid return to a normal diet is the presence of infection. McWhorter, Stout and Lieb<sup>15</sup> found that infected wounds of the stomach and intestines leaked along the suture lines with the slightest increase of intravesicular pressure. Even the breaking strength of an intact diseased bowel, Senn found,<sup>16</sup> was reduced to 1½ pounds (0.75 Kg.) from the normal of from 6 to 10 pounds (2.7 to 4.5 Kg.) per square inch established by Andrews.<sup>17</sup> Early feedings, therefore, should be no larger than absolutely necessary, if infection is suspected.

Attention must be called to the fact that the malnutritions established in these experiments were caused by complete starvation and by partial limitation of an adequate diet over a short period of time. The results, therefore, are only applicable to these two conditions, not to malnutritions arising from other causes. Our conception of the optimum diet for growth is rapidly evolving, and perhaps this diet which we thought adequate here may later prove to be entirely inade-

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15. McWhorter, J. E.; Stout, A. P., and Lieb, C. C.: *The Process of Repair in Wounds of the Small Intestine*, Surg., Gynec. & Obst. **23**:80 (July) 1916.

16. Senn, Nicholas: *Experimental Surgery*, Chicago, W. T. Keener, 1889.

17. Andrews, E. Wyllys: *Pneumatic Rupture of the Intestine, A New Type of Industrial Accident*, Surg., Gynec. & Obst. **12**:63, 1911.

quate. Moreover, we are only beginning to know what constitutes the optimum diet for the healing of wounds.

The effect of complete and partial starvation on the healing of wounds in young rats was quite different from that found in the adults. With complete starvation, life was not maintained long enough for satisfactory determination of the breaking strength of the healing wounds. With partial starvation, healing progressed at the usual rate until the fifth day, and then it definitely became slower. As a result, the entire length of healing time was prolonged.

The explanation of this slowing of the healing rate after the fifth day is difficult. In the adult animals the deficiency of the diet given was compensated for by changes in the endogenous metabolism. Of course, there must have been similar compensating mechanisms in the young. However, because of the greater demands for food for growth, the available food depots were more quickly depleted. Yet, even with this greater demand it is difficult to imagine that the slowing of the rate of healing was caused by a general change in the compensating mechanisms diverting the food substances away from the wound and toward the general maintenance of the body. In the adult rats, it will be remembered there was no such change and healing progressed at the usual rate even until the entire endogenous metabolism was exhausted. A more fitting explanation, then, would be an exhaustion of some food elements or element capable of stimulating and maintaining cellular proliferation, yet not effective during starvation. The answer to these criteria would be a deficiency of vitamins. A deficiency of vitamin B could have been easily established within the time limits of these experiments; it would not have existed during complete starvation, and would not have appeared in such a short time in the adult rats during partial starvation. Besides, the state simulating tetany described for these animals when partially starved is quite similar to the state described for early vitamin B deficiency. Roegholt<sup>18</sup> was disappointed in his efforts to produce change in the rate of healing of epithelial wounds during vitamin A deficiency, but even if he had found such a change, a deficiency of vitamin A could not have been established in less than thirty or forty days. A vitamin A deficiency, then, can be fairly well ruled out. Of course, the relation of the partial deprivation of other food substances in the diet, the proteins and salts, is difficult to evaluate, particularly in their relation to vitamin deficiencies. As far as we know a partial deficiency of proteins or salts does not bring about a difference in the rate of healing because of the compensating

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18. Roegholt, N.: Effect of Vitamin A on Myelopoiesis and the White Blood Picture and Its effect on Wound Healing, *Nederl. tijdschr. v. geneesk.* **2**:3744 (Aug. 10) 1929.

endogenous metabolism, but because the proteins are so necessary for growth and for healing of the wound, and because they are not utilized during a vitamin deficiency, an interrelation of these two food substances is suggested.

We give no apology for this theorizing over the relation of healing of the wound and vitamin deficiencies, because we are, at present, investigating the effect of the vitamins on the basis of this theory. Later we hope to have some definite proof.

Because of the recognized difficulty of interpreting the significance of infections of the wound in rats, a consideration of the different incidences observed on the three diets studied has purposely been omitted. The data were simply accumulated as a matter of routine.

#### SUMMARY

In adult rats the rate of return of healing strength in wounds of the stomach was not appreciably affected by complete starvation. Neither was it affected by giving one-half the required amount of an adequate diet over a short period of time. On the other hand, the healing of wounds in the stomachs of young rats was decidedly retarded by giving only one-half the required amount of an adequate diet. This retardation in healing of the wounds in the stomachs of young rats can possibly be explained by a reduction either separately or in combination of certain elements of the diet. The most probable elements are the vitamins, especially in relation to the deficiency of proteins and salts. The study demonstrated conclusively the remarkable ability of wounds of the stomachs of adult animals to heal in spite of great variations in the amount of food consumed. This ability explains the clinical success of various postoperative dietary regimens which differ in the time when feeding should begin and the amounts of food that should be given.

# SPASTIC PARAPLEGIA IN ACHONDROPLASIA

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In discussing the well known pathologic entity of achondroplasia, the textbooks mention that the disturbance in growth takes place in the bones of the extremities and in those of the pelvis and the skull, and point out that the spine is usually not involved in the process. But it is known that achondroplastic infants are frequently stillborn, and in these cases the spine also may demonstrate marked, even the severest, disturbances of growth, so that the trunk and the extremities together may not be more than one and one-half times the length of the skull. In these cases there is a premature bony union between the vertebral body and the neural arch, bringing about a narrowing of the spinal canal, which is probably the cause of death in the achondroplastic fetus. The foramen occipitale magnum especially seems to be narrow, thus causing a compression of the medulla oblongata.

Generally, there is no marked difference in the length of the spine of an achondroplastic person and that of the spine of a normal person, so that when an achondroplastic person is sitting he may appear perfectly normal (*Sitzriesen*). It is known, however, especially since the investigations of Breus and Kolisko,<sup>1</sup> that the growth of the neural arch in the achondroplastic spine may be markedly disturbed. One sees here a narrowness of the spinal canal, especially in the frontal diameter and in the sagittal diameter. Breus and Kolisko found this to be the case. By measuring two achondroplastic skeletons, Donath and Vogl<sup>2</sup> ascertained that in the same spine the foramina of some segments were narrowed in the frontal direction, others in the longitudinal direction and still others in both directions, to almost the same degree.

Carrying out further investigations on achondroplasia, Donath and Vogl found that there is always a more or less marked change in the physiologic lordosis at the dorsolumbar region, and that only in this region (from the twelfth dorsal to the third lumbar segments) do the bodies of the vertebrae show a more or less pronounced wedging. In their series of seventeen adult achondroplastic dwarfs, they

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From the Department of Orthopedic Surgery, State University of Iowa; Service of Dr. A. Steindler.

1. Breus, Carl, and Kolisko, Alexander: *Die pathologischen Beckenformen*, Vienna, Franz Deuticke, 1900.

2. Donath, J., and Vogl, A.: *Untersuchungen über den chondrodystrophischen Zwergwuchs*, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:333, 1927.



found varying degrees of kyphosis. Another seventeen showed flat backs, and only seven a distinct gibbus. In the light of these findings, the statement of Murk Jansen<sup>3</sup> that achondroplastic patients always have a dorsolumbar kyphosis seems to be exaggerated.

Narrowness of the spinal canal and kyphosis of the dorsolumbar region can bring about a lesion of the spinal cord, depending on the degree of development. These deformities may be so marked that life is incompatible with them, and so death occurs at birth or soon after birth. If there are, however, cord symptoms in an adult achondroplastic patient, these symptoms cannot, as already pointed out by Albrecht and Ranzi<sup>4</sup> and by Donath and Vogl,<sup>2</sup> be due to the spinal deformity alone. The following facts support this statement:

1. There are relatively few cases with lesion of the cord reported as compared to the incidence of spinal deformities.

2. In the few cases that have been reported, the symptoms appeared after bony growth of the spine had stopped. For this reason, the achondroplastic disturbance of growth itself cannot be looked on as the cause of the paraplegia. There must be something more.

#### CASES FROM THE LITERATURE

The following cases, which show a relationship between achondroplasia and neural symptoms, are to be found in the literature.

CASE 1 (Falta,<sup>5</sup> 1913).—A boy, aged 17, presented the following symptoms: ease of fatigue, paresthesia of the lower extremity, flexion contracture of the knees, spasticity and disturbed sensibility from the level of the costal margin downward. Falta ascribed these symptoms to an achondroplastic disturbance of growth.

CASE 2 (Maas,<sup>6</sup> 1920).—A woman, aged 71, was symptomless until the age of 61, when bladder tenesmus and difficulty in walking developed. There were loss of reflexes and hypesthesia in the lower extremities. The author does not give a complete clinical or autopsy report. The photograph of the patient's skeleton seemed to show that there was a definite decrease in the height of the first lumbar vertebra, together with marginal exostoses of the lumbar spine.

CASE 3 (Keményfi,<sup>7</sup> 1924).—An entire family had achondroplasia (the father and eight children). The father showed positive Babinski and Oppenheim signs in later years.

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3. Jansen, Murk: Das Wesen und das Werden der Achondroplasie, *Ztschr. f. orthop. Chir.* **32**:1, 1913.

4. Albrecht, O., and Ranzi, E.: Kompressionsmyelitis bei Chondrodystrophie, *Wien. klin. Wchnschr.* **39**:1241 (Oct. 21) 1926.

5. Falta, Wilhelm: Die Erkrankungen der Blutdrüsen, Berlin, Julius Springer, 1913.

6. Maas, O.: Beitrag zur Kenntnis des Zwergwuchses, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **57**:196, 1920.

7. Keményfi, quoted by Donath and Vogl.<sup>2</sup>

CASE 4 (Albrecht and Ranzi,<sup>1</sup> 1926).—A man, aged 48, was symptomless until 40 years of age, when cramps slowly developed in the lower extremities and paraplegia occurred. He was unable to walk and had become bedridden for a period of one year prior to admission. From time to time he was incontinent. A diagnosis was made of transverse myelitis with a disturbance of sensibility below the first lumbar segment. Roentgenograms of the spine showed a slight kyphosis at the level of the twelfth dorsal vertebra, the height of which was somewhat diminished. The entire lumbar and lower dorsal vertebrae showed marginal exostoses, both anteriorly and laterally. Because the transverse myelitis was thought to be caused by an extramedullary factor, laminectomy of the tenth, eleventh and twelfth dorsal vertebrae was performed. The posterior arches were found to be made up of tough bone, which made their removal difficult. There was no pulsation of the dura, but it protruded markedly from the operative gap, suggesting that the spinal canal was too narrow for the dural sac. At the level of the tenth dorsal vertebra there was found a circular constriction of the dura. An incision was made through the dura below this constriction, which revealed adhesions between the dura and the leptomeninges. There was no tumor, but there was a marked softening of the spinal cord for a distance of about 1.5 cm., corresponding to the constriction. A probe was passed and met with no obstruction. The progress of the patient was remarkable, and improvement was noted on the first day after operation. The retention catheter was removed soon after the operation, and the patient subsequently walked with the aid of tripods.

CASE 5 (Donath and Vogl,<sup>2</sup> 1927).—A man, aged 57, had had a marked gibbus since birth. Six months prior to admission he noticed increased stiffness of the left lower extremity and difficulty in walking. He was incontinent, and tenesmus was present. Later, the right leg became involved, and he was unable to walk. The Wassermann reaction was positive. A diagnosis of a syphilitic process of the spinal cord in the region of the gibbosity was made. Antisyphilitic treatment was given, but without improvement. Laminectomy was refused by the patient. Death at a later date was due to sepsis, arising from a furuncle on the lip. Postmortem examination was performed by Professor Erdheim and showed, among other facts, the following:

To save the spinal cord for microscopic investigation and the vertebral spine for maceration, vertebra for vertebra was disconnected individually and the spinal cord isolated. All of the vertebral foramina were extremely narrow, so that the spinal cord filled the spinal canal completely. At the level of the eleventh dorsal vertebra the spinal cord was somewhat thinned out and softened. There was gray degeneration of the posterior columns; there was a severe angular kyphosis at the region of the twelfth dorsal and first and second lumbar vertebrae. All of these vertebrae were wedge-shaped, especially the first lumbar, the anterior half of which was missing. Its upper and lower surfaces formed an angle of 90 degrees. This deformity brought into contact in their anterior portions the twelfth dorsal and the second lumbar vertebrae, which were also wedge-shaped, though to a lesser degree. These three vertebral bodies showed marked marginal exostoses.

Where the spinal cord was thinned out there was not only narrowing of the intervertebral foramina, as was found in all the other segments, but there was additional narrowing due to the presence of marginal exostoses of the intervertebral joints between the tenth and eleventh dorsal vertebrae. Erdheim believes that these marked arthritic changes arise as a result of the unusually large compensatory range of motion in these joints. There was practically no motion in the area between the twelfth dorsal and the third lumbar vertebrae because of fibrous and even bony fusion of the spinous processes. The articular processes were rudimentary.

CASE 6 (Weger and Nissenbaum,<sup>8</sup> 1929).—A man, aged 40, had a neuropathic constitution, and had shown polynuritic symptoms for a period of three years. The upper and lower extremities, the muscles of the face, the abdomen and the back were involved. There was marked improvement after two months of physical therapy. The authors expressed the belief that the symptoms were due to spondylarthritic changes in the lumbar spine and to the presence of bilateral rudimentary cervical ribs. This is in accord with the views held by Albrecht and Ranzi and by Donath and Vogl.

The six cases cited show a relationship between achondroplasia and neural symptoms of the lower extremities. Of these, only three (the cases reported by Falta, Albrecht and Ranzi and Donath and Vogl) can be considered as typical. The others are not sufficiently well reported to warrant any definite conclusion. The case reported by Weger and Nissenbaum obviously does not belong to this group; it certainly represents a nervous lesion of quite another character. The best contribution is undoubtedly that of Donath and Vogl, because, on the basis of Erdheim's postmortem examination, they cleared up completely the relationship between achondroplasia and the lesion of the spinal cord.

#### AUTHOR'S CASE

The following case is one of chondrodystrophy with paraplegia in which, as in the case of Albrecht and Ranzi, a laminectomy was performed, but unfortunately with less success.

A typical female chondrodystrophic dwarf, aged 21, with marked kyphosis at the dorsolumbar region, was admitted to the hospital in January, 1931. Since April, 1930, she had noticed an inability to lift the left foot off the ground. This symptom became more pronounced; there was marked pain in the left leg, and she noticed a tendency to twitching. On physical examination, a slight atrophy of the left lower extremity and marked spasticity, which was also present on the right side, but to a lesser degree, were found. The knee jerks were hyperactive; there was a definite ankle clonus on the left side. There was disturbance of sensibility for all stimuli. Active motion was markedly diminished on the left side, and there was some impairment on the right. There was no tenderness over the kyphosis. Good control of the bladder and bowel was maintained. These findings suggested a lesion of the third lumbar segment of the spinal cord.

Roentgenologic studies of the extremities and the skull revealed the signs typical of achondroplasia. The spine showed a mild scoliosis to the left in the lumbar region and a marked angular kyphosis of about 90 degrees in the dorsolumbar region, the apex of which was formed by the second lumbar vertebra. The body of this vertebra was distinctly smaller than the adjacent bodies, and it was definitely wedge-shaped. There was slight posterior displacement of this body. The lower anterior portion of the first and the upper anterior portion of the third lumbar vertebrae were in apposition and showed in these areas considerable osteosclerosis and marginal exostoses. A larger marginal exostosis was also seen on the superior surface of the first lumbar vertebra on the right side.

8. Weger, A. M., and Nissenbaum, M. W.: Zur Frage der Erkrankung des Nervensystems bei Chondrodystrophie, *Arch. f. Psychiat.* 87:498, 1929.

On admission, the patient was placed on a frame, and traction was applied to the head with countertraction on the lower extremities. Some improvement was noticed. The reflexes returned to normal, and the cramps in the left calf disappeared. This improvement, however, was only temporary and was followed by recurrence of all the symptoms.

On March 25, 1931, laminectomy was performed. The posterior arches of the twelfth dorsal and first and second lumbar vertebrae were removed. The cord was found to be angulated to about 70 degrees. There was no pulsation. The dura formed a thin transparent membrane which was tight over the cord. A probe passed above and below this point met with no obstacle. The dural sac was not opened.



Lateral roentgenogram, showing the wedge-shaped second lumbar vertebra with its slight posterior displacement. The marked inclination of the first and third lumbar vertebrae, with the marginal exostoses on the anterior side, is evident.

Following the operation, the patient's condition became distinctly worse, and she presented the picture of a flaccid paraplegia. There was no active motion in the lower extremities. Total anesthesia was found in the left leg and on the inner side of the right leg. At this time, the patient complained of severe cramps in both legs. Bowel and bladder symptoms were marked.

Because of these symptoms, it was thought that there might be a hematoma, and the patient was reoperated on, but no hematoma was found. One month following operation the patient showed slight improvement. There was return of some motion in the toes of the right foot and in the flexors of both knees. At a later date, some sensation in both thighs reappeared. In September, 1931, a suprapubic cystotomy was performed because of a purulent cystitis.

At the time of the last examination, in November, 1932, the patient was able to walk on crutches with the aid of two long leg braces, but only a few steps. The retention catheter was still in place.

## COMMENT

This case can be classified as one of typical lesion of the cord in an achondroplastic deformity of the spine. It is difficult, however, for me to believe, as did Falta, that the stenosis of the spinal canal alone is the cause of the lesion of the cord. If Falta's supposition were true, it would be impossible for patients with achondroplasia to survive the period of bony growth of the spine.

The part which the dorsolumbar gibbosity plays in the development of neural symptoms must now be considered. The gibbosity in the case reported by Donath and Vogl, as shown in the lateral x-ray film, was essentially the same as that of my patient. However, in Donath and Vogl's case the gibbosity was at the level of the twelfth dorsal and first and second lumbar vertebrae, while in my case the deformity occupied the area of the first three lumbar vertebrae. In both of these cases the wedge-shaped vertebrae at the apex of the kyphosis showed a slight posterior displacement. As there is already a narrowing of the spinal canal and there is no further space available for the spinal cord to escape any extramedullary pressure, it would seem on first thought that this posterior displacement was the cause of the spastic paraplegia.

There is ample reason to believe that as the patient grows older, posterior displacement becomes more and more marked. Lateral x-ray films of chondrodystrophic children with a marked dorsolumbar kyphosis, as my associates and I have seen in this clinic, show deformities of the body of the vertebra at the apex of the kyphosis. But, at this stage, the vertebra still has an anterior area. On account of the high degree of kyphosis, it can be supposed that this deformed vertebra will later lose its anterior area completely and form instead an anterior edge, as seen in Donath and Vogl's and in my case. It is presumable that posterior displacement goes hand in hand with these changes through the years.

That view also must have been the one held by Donath and Vogl. Furthermore, they believed that a syphilitic process was likely to develop in this area as a *locus minoris resistentiae*. With this supposition of a syphilitic process, it is possible to explain the fact that the sensory changes in their patient corresponded to a lesion of the cord a segment or two above the level of the deformity in the spine itself. (The sensory changes of the body pointed toward a lesion of the second lumbar segment, while the spinal deformity was at the level of the twelfth dorsal and first lumbar vertebrae, which would mean the third and fourth lumbar segments of the cord.)

In my case, the wedge-shaped and slightly posteriorly displaced vertebra was the second lumbar. A compression caused by this vertebra would give rise to a relatively small degree of sensory disturbance, for

at this level there are, normally, the *conus terminalis* and the beginning of the *cauda equina*. But, at the time of admission, my patient already showed sensory disturbances pointing to a lesion above the level of the gibbus.

Consequently, in my case, as well as in the case reported by Donath and Vogl, the clinical analysis indicated a lesion of the cord above the level of the gibbus. Therefore, the lesion of the cord could not have been produced by the wedge-shaped vertebra. Autopsy in their case showed this to be true. There was a compression of the cord due to the projection of marginal exostoses. These marginal exostoses were found protruding from the joints of the vertebrae adjacent to and above the deformity. At this level increased motion had taken place over a long period of time as a compensation for the practically lacking motion at the level of the gibbus, and therefore hypertrophic arthritic changes developed.

Because my case resembles in almost minute detail the case reported by Donath and Vogl, it can be assumed that the same pathologic changes are present as were found in their case at autopsy. Although my patient is still only 21 years of age, there is already definite evidence of *spondylarthritis deformans*, especially of the vertebral bodies at the level of the deformity. In the roentgenogram arthritic changes of the small intervertebral joints are not demonstrable, but that is not remarkable as it is known that these joints are difficult to demonstrate in the x-ray film. One can, therefore, only suppose the presence of arthritic changes in these joints. One cannot prove them. It might be well to emphasize at this point that the passing of a probe without obstruction into the spinal canal at the time of operation is not evidence against the existence of exostoses. The probe was passed posteriorly. The exostoses appear laterally and anteriorly to the cord. In the case reported by Albrecht and Ranzi, too, a probe could be passed without obstruction, but they, nevertheless, thought that *spondylarthritis deformans* was the cause of the lesion of the cord. It is known, from recent observations, that compression of the cord can be caused by marginal exostoses occurring in spines having a canal of normal width; how much more likely is this to happen in the patient with *achondroplasia* who has a narrowed vertebral canal.

The question of therapeutic measures in these cases requires some discussion. In the case reported by Albrecht and Ranzi, certainly in point of deformity one of the mildest, laminectomy was followed by marked improvement of the symptoms. Although there was not complete recovery, the patient could walk again a short time after operation, and he regained control of the bladder and the bowels. In the case reported by Donath and Vogl, the patient refused laminectomy,

but the authors believe, because of the autopsy report, that removal of the projecting marginal exostosis would have given relief of the cord symptoms.

In my case, conservative measures were used first, such as recumbency and traction on head and legs, but without any lasting success. If one accepts as correct the mechanism of the lesion of the cord as previously explained, it is really difficult to understand how a lasting relief could be obtained by conservative means.

Because of the negative result of conservative treatment, laminectomy was finally performed, but unfortunately it did not bring any relief; on the contrary, it induced a flaccid paraplegia with paralysis of the bladder and rectum. It is not possible to give a satisfactory explanation for this fact on the basis of the operative history alone. One can understand that the laminectomy did not improve the symptoms, but why it should bring about a complete transverse myelitis is difficult to comprehend. But, since a serious traumatization of the spinal cord during laminectomy was out of the question, it may be that a minor trauma, as, for instance, sponging, produced the bad result, and that the tissue structure of the spinal cord was certainly softened at the time of operation.

With this explanation, it is still believed that laminectomy is the only therapeutic measure which, on account of the anatomic conditions, gives some hope of improvement. The sooner it can be carried out the better. It should be performed at the region of the deformity and one or two segments higher up. If there are projecting exostoses of the intervertebral joints, they must be removed, and, if possible, a fusion of these points should be performed. The dura mater should be opened in every case and should be kept open. It is not only the good result in the case reported by Albrecht and Ranzi that entitles me to this demand, but especially the result in one of Jaroschy's<sup>9</sup> cases of scoliosis with compression of the spinal cord (these cases of scoliosis are in close relationship to cases of chondrodystrophy). Jaroschy performed in his case, first a simple laminectomy without opening the dura; there was no relief from symptoms after the operation. He therefore reoperated, opening the dura, and the patient showed good recovery from the symptoms.

Finally, one has to consider whether some prophylactic measure could be carried out in cases of achondroplasia with severe dorsolumbar kyphosis. As mentioned, it is to be taken for granted that there is a gradual increase of deformity with the years. The secondary, marked, arthritic changes which may occur in early years are undoubtedly a

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9. Jaroschy, W.: Ueber Spätschädigung des Rückenmarks bei kongenitaler Skoliose und ihre operative Behandlung, Beitr. z. klin. Chir. **129**:348, 1923.

consequence of the abnormal static and mechanical conditions of the spine. In all cases of marked kyphosis in which an increase of deformity can be expected later on, with a possible lesion of the cord, it seems logical to perform a preventive spinal fusion at an early age, if possible in childhood, when most of the chondrodystrophic dwarfs come to medical observation. This fusion might be performed at the whole dorsolumbar region after the method of Hibbs. Removal of the posterior arches of the segments which form the deformity might also be taken in consideration. But whether there is indeed a general indication for this operation, as in some cases of scoliosis, can be established only by careful statistical examination. If these statistics prove that cord symptoms develop later in a high percentage of cases of chondrodystrophy with marked dorsolumbar kyphosis, then this operation would seem to be indicated.



# INTUSSUSCEPTION ASSOCIATED WITH TUBERCULOSIS

## A CASE IN AN ADULT

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The following case of enteric intussusception which recently came under my observation presented some puzzling features, both as to immediate cause and ultimate result:

*History.*—R. O., a man, aged 32, was admitted to Knickerbocker Hospital on April 30, 1932. He was very emaciated and acutely ill. The onset of illness was two days previously, when he suddenly felt a dull pain in the region of the umbilicus. Half an hour later he vomited mucous material, and within a few hours some bright red blood. After that, the vomitus was black. There was no bowel movement for two days. Numerous enemas brought no results. The abdominal pain became sharp after his admission to the hospital. The abdomen was slightly distended, with a boardlike rigidity. No peristalsis was visible. There was tenderness just below the umbilicus, where an indefinite mass was felt. Palpation of the abdomen induced peristalsis and cramps.

The patient gave a history of good health up to the onset of the present illness, except for a bilateral inguinal hernia of some years' duration.

The heart was normal, the lungs clear, and the temperature 100 F.

The symptoms pointed to intestinal obstruction, probably in the lower portion of the ileum, and immediate operation was imperative.

*Operation and Course.*—A right rectus incision was made 6 inches (15.2 cm.) long with the center opposite the umbilicus. The stomach, gallbladder and appendix were normal. There was a 4 inch (10.2 cm.) intussusception of the ileum, 12 inches (30.5 cm.) above the ileocecal junction. The intestine was collapsed below this point and distended above it. This intussusception was reduced by gentle expression and traction, disclosing several bluish and hemorrhagic areas, which were gangrenous. A search for polypi or other tumors which might account for the intussusception was unavailing. The mesentery, however, was unusually long and relaxed and showed a marked absorption of adipose tissue. It gave the impression of a state of extreme ptosis. The mesenteric vessels appeared to have good circulation, and nothing of an unusual nature was discovered except the slight bluish and pallid indurated areas of the intussusceptum, one of which was enfolded with serous suture. There was considerable serosanguineous free fluid in the abdomen.

After reduction of the intussusception, the area was wrapped in hot packs and an enterostomy done about 2 feet above it in the distended portion of the intestine. On reexamination, the condition of the intestine as a whole seemed to have improved greatly since the reduction. A rubber dam drain was placed in the area of the enterostomy, and the abdomen was closed in layers.

Three days after operation the drainage had become profuse, and the drain was removed. The ileostomy was in good condition. The bowels moved only with enemas.

On the following day, the ileostomy tube, which had become loose in the wound, was removed, and the intestinal contents drained freely through the wound. At this time the sutures were cutting into the skin and were removed.

Seven days after operation, the patient was removed to a private room for suction application to the wound. However, this blocked up frequently and allowed the intestinal contents to irritate the edges of the skin. Bronzing liquid and powder were used in combination to prevent this irritation. A collapsible rubber ball and iodoform packing were placed in the sinus, but as this did not prevent leakage, gauze treated with petrolatum was substituted. Every effort to preserve the skin at the edges of the wound proved unsuccessful, and a side-to-side anastomosis was considered, but was temporarily postponed.

A month after operation the patient was losing weight; barium injected through the fistula showed no obstruction, and feeding through the intestinal opening was suggested. At this time there was no evidence of a pathologic process in the lungs except cough, which was thought to be due to excessive smoking.

During the next four weeks the patient continued to lose weight and strength. Blood transfusions were given. On June 29, the abdomen was reopened by Dr. J. V. Bohrer for the repair of the intestinal fistula.

A low, left pararectus incision was made downward 5 inches (12.7 cm.) from the umbilicus. Numerous adhesions had formed, which were easily separated. There was no evidence of the previous intussusception. The fistula was separated from the anterior abdominal wall, and the hole in the intestine was closed with catgut. An entero-enterostomy was then done, short-circuiting the newly closed fistula. This portion of the intestine was lightly attached to the anterior abdominal wall near the former fistula.

On the third postoperative day the wound showed no evident healing. The skin sutures were cutting. The patient vomited a dark, brown fecal-odored material. A Levine tube was inserted to the duodenum; during this manipulation the patient vomited 2,000 cc. of this brown liquid. An enema yielded a liquid return of a brownish color.

A furuncle on the left wrist was incised and drained.

The general condition of the patient became gradually worse, with death on the sixth postoperative day.

*Autopsy.*—Considering the patient's apparently healthy condition prior to the acute obstruction which brought him to the hospital, it was difficult to determine the cause of the intussusception and his lack of resistance to the operation. Fortunately, an autopsy was permitted, which threw some light on the matter, and yet leaves a satisfactory explanation still in the field of conjecture.

A partial report of the examination follows:

The lungs showed chronic, active, bilateral, apical tuberculosis, with bilateral, caseating tuberculous bronchopneumonia in both lower lobes, and tuberculous pneumonia in the left upper lobe.

Parenchymatous degeneration was seen in the liver and kidneys.

Examination of the intestinal tract showed necrosis of the ileum in the region of a recent ileostomy; chronic localized peritonitis of the terminal ileum and ascending colon; ulcerative tuberculous colitis; diverticula of the duodenum, and active tuberculosis of the mesenteric lymph nodes.

The blood vessels of the mesentery were in good condition, but there were marked sclerosis and contraction of the mesentery of the lower portion of the ileum such as occur in cases of old gunshot wounds.

Section through the small intestine disclosed the presence of epithelioid tubercles in the mucosa.

Section through the cecum revealed a small, shallow ulcer of definite tubercle formation, with giant cells in the deeper layers of the mucosa and submucosa.

The report leaves no doubt as to the immediate cause of death, which is stated to be "tuberculous bronchopneumonia, localized peritonitis, necrosis of the ileum and old intussusception." The direct cause of the intussusception, however, still remains in doubt, since there was no neoplasm or tuberculous ulceration at the site of the lesion.

#### ETIOLOGY

An extensive survey of the literature of both tuberculosis and intussusception with their complications has failed to reveal a case similar to the one under discussion. Eliot and Corscaden<sup>1</sup> made a survey of the whole subject of intussusception in adults in 1910, citing 300 cases, in only 10 of which the disease was associated with tuberculosis with ulcer formation or serous or subserous infiltration. In the case herewith reported, the single tuberculous ulceration was confined to the cecum, while the invagination was located in a portion of the ileum a foot from the ileocecal valve and showed no evidence of ulceration. Although a section in this area disclosed epithelioid tubercles in the mucosa, it is highly improbable that this caused the intussusception.

Correspondence with the surgeons particularly concerned in handling cases of tuberculosis at the nearby hospitals brought to light no instances of intussusception in recent years associated with tuberculosis such as the one herewith reported or those reported by Eliot and Corscaden.

Rubin<sup>2</sup> collected the reports of 500 autopsies on patients who had died of pulmonary tuberculosis, viewed with special reference to the condition of the intestines. Macroscopic ulcerations were revealed in the intestines in 324 of the 500 cases, ranging from a few incipient lesions to an extensive involvement of the whole intestinal tract. Yet, there is no mention of an intestinal intussusception in the whole list.

In view of these facts, pulmonary tuberculosis as a direct cause of intussusception is difficult to establish. But there is no doubt that it constitutes a predisposing factor. Gastro-intestinal disturbances have been noted by various observers in from 70 to 92 per cent of the cases of early tuberculosis. In the acute forms they are always present to a marked degree. As the disease progresses and emaciation becomes more and more pronounced, evidence of enteroptosis with

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1. Eliot, Ellsworth, and Corscaden, James A.: Intussusception with Special Reference to Adults, *Ann. Surg.* 8:169 (Feb.) 1911.

2. Rubin, E. H.: Pulmonary and Secondary Intestinal Tuberculosis, *Am. Rev. Tuberc.* 22:184 (Aug.) 1930.

atony of the stomach is increasingly seen. In cases of moderate severity, in which there is little or no secondary invasion of the gastro-intestinal tract by the disease, the abdomen is unusually soft, relaxed and extremely tender. A gastric catarrh is by this time almost always present. The gastric contents show a high degree of both motor and secretory insufficiency, the gastric acidity being greatly reduced. The bowels also are commonly affected, first by constipation and later by occasional severe attacks of diarrhea which increase in frequency and cause intense weakness and exhaustion.

Thus there is a condition of lessened resistance throughout the gastro-intestinal tract, inviting disaster, as it were, from the impact of any unaccustomed shock or strain to which it may be subjected.

Among the direct causes of intussusception in the adult, in the small intestine, by far the most common is the presence of a polyp, benign tumor or foreign body; in the large intestine, on the contrary, it is usually a malignant tumor. The neoplasms are usually found at the apex of the intussusceptum and are pedunculated in form.

Ulcers arising from typhoid fever or intestinal tuberculosis are frequent causes, as are paralytic conditions of the intestine which allow the collapse of one portion into another.

Trauma is considered by some authorities an important causative factor. Strong movements of the muscles as in severe coughing, falls from a height, heavy lifting and football playing are given as instances.

Diet appears to play an important part. Orr<sup>3</sup> cited the case of an Indian coolie 30 years old, very thin and poorly nourished, who came to the hospital with an enteric intussusception involving 3 feet of the ileum. After resection and side-to-side anastomosis, a second large intussusception formed in a proximal portion of the intestine. Even after this was reduced there were violent and irregular peristaltic movements passing along the intestine as if another intussusception were attempting to form. In the absence of anything in the abdomen to suggest a cause for the intussusception, it was attributed to the patient's defective diet, which had consisted of tapioca, rice water, tamarind and red chillies, with occasional small quantities of fish.

Contrary to the rule elsewhere, in India there seems to be a predominance of cases in adults over those in infants. In one hospital 66 per cent of the cases occurred in persons over 20 years old. In only two of these was there any record of a polyp or structural defect. Some upset in the neuromuscular control of the bowel, probably due to faulty diet, seemed indicated in the rest.

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3. Orr, Ian M.: An Unusual Case of Intussusception in an Adult, *Brit. M. J.* 1:331 (Feb. 20) 1932.

The direct effect of an improper food balance was shown by McCarrison in his experiments on monkeys. These were put on a regimen deficient in vitamins, low in proteins and high in carbohydrates. Among other changes in the gastro-intestinal tract, a very high percentage of intussusception was noted. From this, Dr. McCarrison<sup>4</sup> traced a definite causative relationship between dietetic insufficiency and intussusception. "No doubt there is nothing new in such a statement," he observed, "but I do not think we have realized hitherto that the neuro-muscular control of the bowel is dependent in great measure on the adequate provision of vitamins in the food."

The use of castor oil as a household remedy is held by some authorities to be largely productive of intussusception, owing to the strong, irregular peristalsis it induces. Kock and Orum<sup>5</sup> believed this to be the reason for the numerous cases found in Great Britain and Denmark as compared with France and Germany, where it is less widely used.

Owing to the difference in diameter of the small and the large intestine, the ileocecal or ileocolic type of intussusception is by far the most frequent. In a wide survey, Perrin and Lindsay<sup>6</sup> found the ratio between this and the enteric type to be about 6:1. In the absence of definite etiologic factors, they considered the cause of enteric intussusception probably to be found in the swelling of a Peyer's patch. Briefly formulated, their theory to account for a majority of primary intussusceptions is the production of the equivalent of a foreign body within the wall of the intestine. This foreign body is provided by the swelling of a preexisting lymphoid tissue. The anatomic and age distribution of the lymphoid tissue in the alimentary canal agrees exactly with the anatomic and age distribution of all primary intussusceptions. Hence children are more liable. The factor that provokes this swelling is usually some gastro-intestinal disturbance, with resulting chemical irritation; the formation of gas from indigestible foods, such as cabbage and sausage, may be sufficient to cause it.

Another possible cause of intussusception is tuberculosis of the mesenteric lymph glands. This condition is a definite clinical entity. It is found to occur most commonly between the ages of 20 and 30. The patients are, as a rule, not of the rugged type, but rather slender, poorly nourished and anemic; they tire easily, have lost weight or fail to gain in weight.

Despite its frequency, little attention has been directed to this disease, and its surgical significance is seldom recognized in connection with abdominal operations.

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4. McCarrison, quoted by Orr.<sup>3</sup>

5. Koch, A., and Orum, H. P. T.: *Bibliot. f. læger* **12**:333, 1911.

6. Perrin, W. S., and Lindsay, E. C.: *Intussusception*, *Brit. J. Surg.* **9**:46 (July) 1921.

The enlargement of the mesenteric glands, through this infection or otherwise, is recognized as a cause of various gastrointestinal symptoms, among which are pain, tenderness, rigidity and perhaps a slight rise in temperature; also colicky dysfunctions of the digestive tract, pyloric spasm, spasticity of the abdominal muscles and nervous irritability, which probably arise reflexly from irritation of the autonomous nerves by the enlarged glands.

Alvarez<sup>7</sup> stated that it seems probable that many of the strange disorders of digestion associated with slight fever, nausea, abdominal soreness, signs of reverse peristalsis and diarrhea could best be explained on the basis of such a low grade tuberculous infection of the lymph nodes. In his opinion, one of the greatest needs of medicine today is some means of raising the resistance of the body to such infections. He suggests that symptoms of this sort be treated exactly as if they were known to be of tuberculous origin, i. e., by rest, over-feeding and heliotherapy.

An enlarged tuberculous lymph gland can directly produce intussusception by pressure into the wall of the intestine, forming a pocket which grows gradually deeper under the peristaltic movements of the bowel until there is a complete invagination, with the lymph node enfolded at the apex of the intussusceptum. This process has been graphically shown by Lorenz<sup>8</sup> in the case of a small mesenteric cyst which, pressing into the ileum, forced its way through the ileocecal valve and produced a deep ileocecal intussusception.

Sherman<sup>9</sup> reported the case of a child showing every symptom of intussusception. When the abdomen was opened, a much enlarged tuberculous lymph gland was found lying close enough to the spine to press against the mesenteric veins and partially occlude them. The intestine served by these obstructed veins was thick, edematous and congested. While no intussusception was found in this case, it may be said that the stage was all set for such a catastrophe, which doubtless would have occurred had not resection of the affected portion of the intestine with its mesentery been promptly done.

All stages of tuberculosis may be found in the mesenteric lymph glands—tubercles, caseation, liquefaction and all degrees of calcification.

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7. Alvarez, Walter C.: Mesenteric Lymphadenitis in Adults, Cause of Pseudo-Appendicitis, Indigestion, Diarrhea and Arthritis, *M. Clin. North America* **14**:605 (Nov.) 1930.

8. Lorenz, Hans: Ein Beitrag zur Lehre von der Invagination, *Deutsche Ztschr. f. Chir.* **77**:7, 1905.

9. Sherman, Harry M.: Tuberculosis of Mesenteric Lymph Glands, Symptoms of Intussusception Necessitating Resection of the Intestine, *California State J. Med.* **4**:43, 1906.

According to Ross Golden,<sup>10</sup> the complications which may follow are: (1) adhesions from the nodes to the intestine or to the abdominal wall, which may produce ileus; (2) pressure on other structures, such as the stomach or the ureter; (3) perforation of a caseous node into the peritoneal cavity, and (4) generalized miliary tuberculosis. The symptoms of these may entirely mask the original disease. While Golden makes no mention of intussusception as a sequel, its probability may legitimately be inferred.

Tuberculosis may exist in the mesenteric lymph glands without tuberculous involvement of other organs. In the gastro-intestinal tract bacilli little affected by the gastric juices pass readily through the stomach, where little absorption takes place, with no apparent weakening of their virulence. They pass rapidly through the duodenum and jejunum, where the food, mixing with digesting fluid, is being prepared for use. In the ileum the first effective absorption of the contents of the alimentary canal naturally occurs. There, as in the case of typhoid bacilli, tubercle bacilli pass the epithelial barrier to the submucosa and act on the solitary follicles or Peyer's patches, and make tubercles in the mesenteric nodes. Brown and Sampson<sup>11</sup> have shown little mammilations giving evidence of healed lesser grades of tuberculous infection of the lymphoid structures of the submucosa of the small intestine. Auchincloss<sup>12</sup> stated that he has often looked for gross evidence of scarring in the intestinal walls, but found none. It is probable that most cases of tubercle bacillus infection of the mesenteric glands show no evidence of disease in the intestinal wall.

In an adult, these diseased glands may be the cause of ill health existing from childhood. On the other hand, in many cases clinical symptoms do not develop and may be discovered only when the patient is being examined for another disease. Such lesions seems to indicate a handicapped area in one of the most important functioning sections of the body, and when the individual as a whole, or the area in particular, is subjected to excessive stress or activity or infection, it will not function; it breaks down, and so-called intestinal symptoms appear.

The lymph and lacteal drainage for the corresponding part of the intestine has been diseased beyond repair. The node has been walled off as a foreign body as nearly as possible. A rearrangement and compensatory mechanism have had to be established, the efficiency of which is

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10. Golden, Ross, and Reeves, R. J.: Significance of Calcified Abdominal Lymph Nodes, *Am. J. Roentgenol.* **22**:305 (Oct.) 1929.

11. Brown, Lawrason, and Sampson, H. L.: *Intestinal Tuberculosis*, ed. 2, Philadelphia, Lea & Febiger, 1930.

12. Auchincloss, Hugh: A Clinical Study of Calcified Nodes in the Mesentery, *Ann. Surg.* **91**:401 (March) 1930.

generally less than that of the original arrangement. The same is true of the blood vessels to and from the lymph nodes and adjacent to them. Damage may have occurred to the sympathetic nerve trunks in the region, impairing their nutrition and giving rise to symptoms that may be spastic or paralytic.

The facts here presented afford a framework into which the clinical picture of the case under discussion may be found roughly to fit.

A weak, undernourished man suffered from active tuberculosis of the lungs, which alone would tend to lower the resistance of the gastrointestinal tract, as has been shown, and make him liable to serious consequences under any unusual stress or strain. The enlarged tuberculous mesenteric lymph glands were capable of causing invagination by pressure into the intestinal wall, or by pressure on the sympathetic nerve trunks producing paralysis of the intestine. His mesentery was long and markedly lacking in fat, and the stomach and intestines probably atonic and ptosed—a condition peculiarly favorable to ileus, either through volvulus or intussusception. The question is, what took place in this area in which every preparation seems to have been made to bring about the final catastrophe—intussusception?

It may have been, as Perrin and Lindsay suggest, a swelling of the Peyer's patches which acted as a foreign body. In the light, however, of new facts in the patient's history which have just come into my possession through the kindness of his widow, I believe the determining cause more likely to have been trauma.

The patient was a waterproofer by trade, and had returned to his work just two days before the onset of his illness, after driving a taxicab for a year. He was a small man averaging 126 pounds (57.2 Kg.) in weight, and "soft" when he returned to this job. Far from being in good health, as he stated, he had coughed a great deal during the previous winter, especially in connection with heavy smoking, was constipated, and had night sweats.

His appetite was good, in fact, he was "always eating something." Certain foods, however, made him vomit.

Three or four days before the onset of his illness, he ate some cabbage, which upset him as it always did.

The patient was in a weakened condition when he took up his work as waterproofer. His duties required him to lift heavy pails of tar weighing about 75 pounds (34 Kg.), one in each hand. On April 28, just two days before he came to the hospital, he almost fainted from this exertion and experienced a sudden pain in the abdomen. He was so ill he had to be helped off the job and taken to a first aid station, where he was given some paregoric. After eating sausage for lunch, he felt very sick and took some castor oil and magnesium sulphate. He did not use castor oil habitually, but relieved his constipation with a patented preparation of phenolphthalein.

After taking the castor oil and magnesium sulphate, the patient began vomiting red blood, and summoned a doctor, who, believing the symptoms to be those of gastric ulcer, treated him accordingly. Two days later he came to the hospital and the intussusception was discovered.



The fact that his illness came on in the act of lifting a heavy weight makes it appear that this unaccustomed strain was the final, direct cause of the intussusception. Eliot reports in his series seven such instances.

In view of the patient's general pathologic condition, the fatal outcome was perhaps not surprising. It may be open to question whether immediate resection and anastomosis would have shown better results.

Oschner<sup>13</sup> observed that the treatment in any case of acute obstruction depends on the amount of distention in the afferent loops, the degree of interference with the vascular supply of the part, and the condition of the patient. In the presence of marked distention of the intestine proximal to the obstruction, no attempt should be made to remove the pathologic process producing obstruction, since the contents of the intestine are extremely toxic and contain highly virulent organisms. The distended intestine is thinned and very friable. Resection of the pathologic process with reconstruction of the intestinal tract is not feasible. The sutures introduced into the distended pathologic wall of the bowel are insecure. The operative procedure requires more time than is warranted by the patient's condition. Any operative procedure should involve merely the relief of the obstruction. At a later date, as soon as the patient has recovered from the toxemia and signs of acute obstruction, the cause may be removed. The obstruction is best relieved by production of a fistula either by enterostomy or colostomy. This should be made immediately above the obstruction.

There is probably no one condition the surgeon encounters which causes him more concern than certain cases of ileus. Even in spite of the most careful and exacting therapy the condition often progresses to a fatal termination.

The mortality in acute obstruction is high. Van Beuren and Smith,<sup>14</sup> in a series of 349 collected cases, demonstrated an average mortality of 60.7 per cent after enterostomy. Wichmann<sup>15</sup> stated that in 223 cases of intussusception, nearly 70 per cent of the patients died after operation. Perrin and Lindsay, however, place the mortality rate much lower, their average in 400 cases being given as 34.7 per cent.

In discussing the cause of death from high obstruction, Hartwell and Cooper<sup>16</sup> said:

It is apparent that the cause of death following intestinal obstruction is the absorption of toxic substances into the blood. The source and nature of these substances are not fully established, nor is it certain what rôle is played by the loss

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13. Oschner, Alton, in Nelson Loose-Leaf Living Surgery, New York, T. Nelson & Sons, 1927, vol. 5, p. 266.

14. Van Beuren, F. T., and Smith, B. C.: Status of Enterostomy in Treatment of Acute Ileus, *Arch. Surg.* **15**:288 (Aug.) 1927.

15. Wichmann: *Deutsche Ztschr. f. Chir.* **77**:1, 1905.

16. Hartwell, John A., and Cooper, Henry S. F., in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 7.

of substances, particularly water and chlorides, in the vomitus, but this is doubtless an important factor.

What is the cause of death in high obstruction? No theory of toxemia has given rise to any practical means of preventing death after the condition has fully established itself. Surgical intervention is the best means, and only too often this is of no avail. We do not know the cause of death from high obstruction. It is to be hoped that somebody will find the answer and bring light where there is now darkness.

#### SUMMARY

Intussusception is much less frequent in adults than in children. Approximately twice as many males as females are affected by it.

The mortality is high, being in direct ratio to the length of time after the appearance of symptoms that operation is done. There is a decided tendency to recurrence even after resection of the portion of bowel originally affected. Spontaneous recovery sometimes takes place, the necrotic intussusception becoming detached and passing through the bowels.

The disease constitutes a grave threat among persons suffering from other diseases, notably typhoid fever and tuberculosis. It is induced by such conditions as undernourishment, radical changes of diet creating hyperperistalsis, visceroptosis, mesenteric lymphadenitis, and tumors, cysts, ulcers and adhesions in the gastro-intestinal tract, while trauma undoubtedly plays an important part in many cases as an activating agent.

In cases of pulmonary tuberculosis it is a complication to be feared, since it may not only lessen the possibility of recovery by interfering with the patient's nutrition, but in its acute form is more than likely to precipitate a fatal termination. On the other hand, pulmonary tuberculosis, with its weakening effect on the gastro-intestinal tract, predisposes the patient to intussusception.

Undernourishment, through insufficient or ill balanced diet, is a definite causative factor, and perhaps the only one through which effective preventive action may be taken.

It is suggested that every tuberculous patient be regarded as a potential victim of intussusception, and his treatment planned with this complication in view. This may mean simply an intensification of the regular treatment for tuberculosis, with special emphasis on over-nutrition, protection from overexertion and an increased watchfulness for gastro-intestinal symptoms.

# DIAGNOSIS AND TREATMENT OF FRACTURED SKULLS

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A newly awakened and much needed scientific interest in the study of fractured skulls and intracranial injuries is evidenced by the rapid increase in the literature on this subject in the past five years. It is clear to us that there are many imperfections in our knowledge of the basic pathologic and physiologic changes that are present in these cases, and only after these gaps in our knowledge have been filled shall we be able to interpret correctly many of the clinical phenomena observed daily in the wards. A much better understanding and correlation of fundamental facts are needed to put us on the right track. Each writer has his own classification, which varies with his concepts, and this results in much confusion and controversy and renders comparative work difficult, because one is never quite sure that one author is writing about exactly the same thing that another author has described. Many of the differences are more apparent than real and are due to inability to understand one another, while, on the other hand, some are definite disagreements in fundamental ideas. It is our purpose in this paper not to offer a solution to these problems, but to report our experiences in the study and management of these cases at Harlem Hospital, and to draw certain seemingly justified conclusions therefrom. This work is supplemental to and a continuation of the studies made at Harlem Hospital by Dr. John F. Connors,<sup>1</sup> surgical director, which were reported by him in two separate papers, based on a study of a total of 833 cases. In our present work we were fortunate in having the benefit of his advice and supervision.

We studied 347 consecutive cases of cranial and intracranial injuries, as the patients were admitted to the wards, from Sept. 1, 1930, to April

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From the Surgical Service of Harlem Hospital, Dr. John F. Connors, Director.

Presented before the Joint Meeting of the Boston, New York and Philadelphia Regional Fractures Committee of the American College of Surgeons, New York, May 19, 1932.

1. Connors, John F.: Management of Intracranial Injuries With or Without Fracture, *Ann. Surg.* 81:901, 1925; The Treatment of Fractures of the Skull, *Tr. Am. S. A.* 14:427, 1927.

20, 1932. From Sept. 1, 1930, to Oct. 1, 1931, we diagnosed all severe craniocerebral injuries as "clinical fractured skull," which is the classification in general use today, but the conviction gradually grew on us that only cases in which we could actually prove the presence of a fracture or fractures by roentgen examination or autopsy should be so diagnosed or classified; therefore, beginning on Oct. 1, 1931, we divided the lesions into two groups according to whether or not a fracture of the skull had been demonstrated: (1) proved fractures of the skull and (2) proved intracranial injuries without fractured skull. It is common knowledge that the treatment of fractured skulls is concerned chiefly with the treatment of the concomitant underlying injury to the brain or its coverings. We were careful to exclude all cases with questionable or only suggestive roentgenograms from our group of proved fractures of the skull. When there was a history of trauma, blood in the spinal fluid was the basis for making a diagnosis of intracranial injury in patients who lived, and of course for an autopsy in

TABLE 1.—*Classification of Cases*

	Number of Cases	Lived	Died	Mortality, per Cent
Class A. (Sept. 1, 1930, to Oct. 1, 1931)				
Clinical fractures of the skull; includes intracranial injuries .....	129	99	30	23.2
Class B. (Oct. 1, 1931, to April 20, 1932)				
Group 1. Proved fractures of the skull.....	133	93	35	26.3
Group 2. Proved intracranial injuries .....	85	77	8	9.4
Total.....	347	274	73	21.0

fatal cases. Blood in the spinal fluid owing to a ruptured aneurysm of one of the vessels of the circle of Willis occurred in rare instances (an average of about 1 such case a year). Before we made a clinical diagnosis of intracranial injury without skull fracture, we satisfied ourselves that the blood in the spinal fluid was not due to contamination resulting from the lumbar puncture. We excluded from the group of those with intracranial injury without fracture of the skull 53 patients who had been sent to the wards with the diagnosis of "possible fractured skull" or "head injury." A history of trauma was given by most of them, and a history of unconsciousness by all of them; but the results of roentgen examination were negative, and the spinal fluid was devoid of red blood cells. We realize that we may have missed 1 or 2 cases of slight cerebral injury by insisting on the presence of blood in the spinal fluid before permitting this diagnosis to be made. None of the innumerable patients with simple laceration, contusion and hematoma of the scalp who come to the hospital were included in this study, as they were treated in the emergency room of the hospital and sent home. All cases in this series were grouped as shown in table 1.

It is seen that the incidence of actual fractured skulls is much higher than the incidence of intracranial injuries without fractured skull and, too, that the mortality from intracranial injuries without fracture of the skull is only about one-third the mortality from real fractured skull.

A clinical diagnosis of fractured skull should not be made unless the existence of the fracture is proved by roentgen examination or the fracture is actually seen, as is possible in certain compound fractures or at operation. A clinical diagnosis of intracranial injury should be made only after red blood cells are found in the spinal fluid. Erythrocytes in the spinal fluid constitute the chief tangible and the most trustworthy evidence of injury that is available at the present time, and the tendency to accept this view is shown by the fact that Kennedy and Wortis<sup>2</sup> in a recent review of 1,000 cases of "head injuries" used the same criteria. The term "head injury" should be discarded as it is too indefinite, and although what it means today is known, it could properly include traumatisms of the face and scalp. Either there is a fracture of the skull or there is not, and either there is intracranial injury without fracture or there is not; and both conditions exhibit pathologic changes that are demonstrable clinically.

Acute alcoholism coexists so frequently with injuries of this type and in so many instances obscures the clinical picture irrespective of the degree of trauma that it becomes a factor of no inconsiderable importance. Vance<sup>3</sup> found alcohol in the liver and brain in 512 fatal cases. It was noted by McCreery and Berry<sup>4</sup> in their clinical study of 520 cases, but they could not estimate its importance. In our group of cases, a diagnosis of acute alcoholism as an associated condition was made in 54 instances, or 18.8 per cent, and we feel that the percentage is much too low, because in many of the unconscious patients the effects had worn off before we saw the patients or were masked by the concomitant injury. Alcohol can and does produce disorders of consciousness, as well as retrograde amnesia; and these two symptoms, particularly the loss of consciousness following cephalic trauma, are the most important of those produced by acute craniocerebral injury. In fact, the diagnosis of cerebral concussion is based entirely on the history, or on the presence, of loss of consciousness following trauma. We are of the opinion that alcohol plays a much larger rôle in these cases than is generally thought, and that it accelerates death in many instances, owing to its late depressant effects on all body functions.

2. Kennedy, Foster, and Wortis, S. Bernard: Head Injuries, *J. A. M. A.* **98**:1352 (April 16) 1932.

3. Vance, B. M.: Fractures of the Skull, *Arch. Surg.* **14**:1023 (May) 1927.

4. McCreery, John A., and Berry, Frank B.: A Study of 520 Cases of Fractures of the Skull, *Ann. Surg.* **88**:890, 1928.

Much further work is necessary to determine exactly the part that alcohol plays in these cases.

The nature of the trauma is shown in table 2. Gunshot wounds ordinarily would fall into the category of assaults, but it seemed desirable to group them separately. In the group with the "history of injury unknown" the lack of the history may be explained by death without recovery of consciousness, alcohol and retrograde amnesia. Many of these patients were found unconscious in hallways or arcaways; and in not a few cases patients brought to the hospital died, and we were not able to identify them. Today the automobile is the leading causative factor in the production of fractured skulls.

As regards sex, the ratio of males to females in this series was about 3 to 1.

There were 28 children under 10 years of age, and 1, or 3.5 per cent, died. The patient that died was an infant of 2 months who was struck with a bottle and sustained a fracture involving the right frontal sinus; death occurred four days later as a result of meningitis. Our

TABLE 2.—*Nature of the Trauma in Intracranial Injuries*

	Our Cases	Connors' Cases
Automobile .....	120	115
History of injury unknown.....	87	49
Falls .....	77	133
Assaults .....	55	27
Gunshot wounds .....	3	0
Street cars .....	3	17
Subway cars .....	2	5

observations in general confirm the conclusions of Beekman,<sup>5</sup> Ireland,<sup>6</sup> Wakeley<sup>7</sup> and others relative to the better prognosis for life in cranio-cerebral traumatisms in children.

The time elapsing between admission to the hospital and death in the 73 fatal cases is shown in table 3.

It is seen that 38 patients, or 52 per cent, died within the first twelve hours. Fay<sup>8</sup> reported that 12 of 39 deaths occurred within three hours after admission to the hospital in one of his series, while McCreery and Berry recorded that 110 of 204 deaths occurred within the first twelve hours after admission. Death after forty-eight hours in most instances was due, not to laceration of the brain, but rather to a complication, such as meningitis, hypostatic pneumonia, associated injury, or exhaus-

5. Beekman, Fenwick: Head Injuries in Children, *Ann. Surg.* **87**:355, 1928.

6. Ireland, Jay: Fracture of the Skull in Children, *Arch. Surg.* **24**:24 (Jan.) 1932.

7. Wakeley, Cecil P. G.: Fractures of the Skull in Children, *Practitioner* **127**:75 (July) 1931.

8. Fay, Temple: Clinical Considerations Surrounding Head Injuries, *S. Clin. North America* **11**:1375 (Dec.) 1931.

tion and inanition. This was first pointed out by Connors, and the chief exception to this rule has been extradural hemorrhage. Death due to laceration of the brain and subdural hemorrhage usually occurs within forty-eight hours after the injury, and if death does occur later it is the exception to the rule, as happened in a case in our series.

Cerebral concussion is the term used to denote the unconsciousness that occurs after an injury to the head, and is not usually associated with fracture of the skull, in the clinical acceptation of the word. There is much controversy among observers in explaining exactly what happens and whether or not it has a pathologic basis in fact. Vance listed 27.4 per cent of the deaths in his series as due to concussion, and in some he could find no pathologic basis; all of his patients died within a few minutes or hours after the injury. Ochsner<sup>9</sup> expressed

TABLE 3.—*Time Between Admission to the Hospital and Death*

Time in Hospital Before Death	Class A	Class B	
	Clinical Skull Fractures	Group 1 Skull Fractures	Group 2 Intracranial Fractures
1 hour .....	1	8	2
3 hours.....	2	4	1
6 hours.....	5	3	1
12 hours.....	6	5	0
24 hours.....	3	4	0
2 days.....	4	2	0
3 days.....	2	2	1
4 days.....	4	4	1
5 days.....	1	0	1
6 days.....	0	1	0
8 days.....	0	1	0
9 days.....	1	0	0
12 days.....	1	0	0
14 days.....	0	1	0
20 days.....	0	0	1
Total number of cases.....	30	35	8

the belief that concussion is "a physiologic and not an anatomic lesion," while Riddoch<sup>10</sup> stated that it "may produce death presumably from bulbar anemia." Ritter and Strebel<sup>11</sup> described concussion of the medulla and concussion of the cerebrum. On the other hand, Rand and Courville<sup>12</sup> found edema of the choroid plexus in 2 cases. Peet<sup>13</sup> thinks that there are probably minute lacerations of the brain substance.

9. Ochsner, Alton: The Diagnosis and Treatment of Acute Craniocerebral Injuries, *Am. J. Surg.* **12**:222 (May) 1931.

10. Riddoch, George: Discussion on the Diagnosis and Treatment of Acute Head Injuries, *Proc. Roy. Soc. Med.* **25**:735 (March) 1932.

11. Ritter, A., and Strebel, K., quoted by Ochsner.<sup>9</sup>

12. Rand, Carl W., and Courville, Cyril B.: Histologic Studies in Cases of Fatal Injury to the Head, *Arch. Surg.* **23**:357 (Sept.) 1932.

13. Peet, Max Minor: Symptoms, Diagnosis and Treatment of Acute Cranial and Intracranial Injuries, *New York State J. Med.* **28**:555 (May 15) 1928.

Dr. C. S. B. Cassasa,<sup>14</sup> one of our associates, in 1925 found minute hemorrhages into the perivascular lymph spaces in 5 cases that exhibited clear spinal fluid. Kaufmann<sup>15</sup> stated: "That gross damage is done, such as multiple hemorrhages (tearing of vessels through shock or the push the brain substance resists), is shown by the fact that foci of white softening appear as an expression of the microscopic damage to the nervous tissue, to which may be added petechial hemorrhages." Jefferson<sup>16</sup> expressed the belief "that in all head injuries serious enough to call for treatment during the acute stage, there is a fundamental state due to general cerebral contusion and that this has a recognizable histological picture." He has also observed the minute hemorrhages first described by Cassasa. He would discard the use of the term concussion, and we agree with him that its use adds confusion; we also agree with him that any patient who on admission to the hospital is unconscious may be safely assumed to have definitely widespread neural damage, although we qualify the latter statement by specifying that the unconsciousness must be due to trauma and not to alcohol or drugs. It seems clear that Cassasa, Jefferson and Kaufmann have described the same pathologic condition under different names—they are all agreed that unconsciousness of sufficient degree and duration to require hospitalization has associated pathologic changes in the central nervous system, whether the latter are demonstrable or not, and it is with this idea that we are in accord. If the term concussion is to continue in use, the description of the clinical features as outlined by Trotter<sup>17</sup> should be used, which is as follows: (1) instantaneous onset, (2) paralytic nature of the symptoms and (3) a tendency to disappear spontaneously. To these we would add: (4) a history of trauma and (5) the elimination of alcohol and drugs and other diseases.

Contusions of the brain were not mentioned by Vance. LeCount and Apfelbach<sup>18</sup> described them as "contre-coup bruises," and found them in 49.2 per cent of their cases. Jefferson defined the term contusion as "a general contusion of the whole brain," which is apparently what Vance, under the term concussion, called a "jarring of the brain":

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14. Cassasa, Charles S. B.: Multiple Traumatic Cerebral Hemorrhages, *Proc. New York Path. Soc.* **24**:101, 1924.

15. Kaufmann, Edward: *Pathology for Students and Practitioners*, translated by Stanley P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1914.

16. Jefferson, Geoffrey: Discussion on the Diagnosis and Treatment of Acute Head Injuries, *Proc. Roy. Soc. Med.* **25**:742 (March) 1932.

17. Trotter, Wilfred: The Scalp, Skull and Brain, in Choyce, C. C., and Beattie, M.: *A System of Surgery*, New York, Paul B. Hoeber, Inc., 1923, vol. 3, p. 446.

18. LeCount, E. R., and Apfelbach, Carl W.: Pathologic Anatomy of Traumatic Fractures of the Cranial Bones and Concomitant Brain Injuries, *J. A. M. A.* **74**:501 (Feb. 21) 1920.



and Jefferson stated further that he implied "punctuate hemorrhages of greater or less extent." It seems that he includes the Cassasa type of hemorrhage also under this heading. Connors described contusion as "small hemorrhages in the pia arachnoid meshwork; and the patients have a bloody spinal fluid, but it is not as bloody as in laceration of the brain." Connors and McClure and Crawford<sup>19</sup> found contusion to be less frequent clinically than concussion, and this has been our experience. Under this heading we include all cases of subarachnoid or subdural hemorrhage without laceration of the brain. Subdural hemorrhage was present in 95 per cent of LeCount and Apfelbach's cases, and was most frequently due to lacerated cerebral veins.

Laceration of the brain has been the most common pathologic finding. It occurs with or without marked hemorrhage in all cases of severe trauma, and the spinal fluid is bloody. Lacerations may occur at the point of injury, or they may be contre-coup; contre-coup lacerations are the most frequent. The clinical symptoms in general in these cases are due to cerebral compression resulting from hemorrhage rather than from the laceration itself. Vance reported 132 deaths from cerebral compression and 24 deaths from laceration of the brain in his series. LeCount and Apfelbach did not use the term laceration, but spoke of such lesions as extensive bruises, and in a published photograph of a brain that exhibits a large laceration, they called the lesion a bruise. Apfelbach<sup>20</sup> in a later study found that the hemorrhage in contusion is greater the longer the patient lives, and thought that this is due to the persistence of the bleeding after the injury. This is true as regards lacerations of the brain, as shown by the fact that in some cases the spinal fluid may be clear immediately after an injury, whereas after a few hours it contains blood. We have yet to see a case of laceration of the brain in which the spinal fluid is persistently clear; in the vast majority of cases the fluid is bloody on lumbar tap immediately after the injury.

Extradural hemorrhage is due to a laceration of the middle meningeal artery or one of its branches in most instances, but Vance found rupture of the lateral sinus in two cases. He stated "that it occurs in thin skulls and the sharp edge of the bone lacerates the wall of the vessel." Epidural hemorrhage was present in 20 per cent of Vance's necropsies, and it was a death-causing factor in about 10 per cent of the necropsies which LeCount and Apfelbach reported, according to their opinion. In 1 of every 10 fatal cases epidural hemorrhage is the cause of death. A fracture is always present, and the vessel ruptures in almost all cases at the intersection of the path of the vessel and the

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19. McClure, R. D., and Crawford, Albert S.: The Management of Cranio-cerebral Injuries, *Arch. Surg.* **16**:451 (Feb.) 1928.

20. Apfelbach, C. W.: Studies in Traumatic Fractures of the Cranial Bones, *Arch. Surg.* **4**:434 (March) 1922.

line of fracture. This is important when one operates on these patients. In only a single case in this series did the patient show the lucid interval usually described.

Cerebral edema is generally considered to follow immediately all severe cranial and intracranial injuries. The modern treatment of intracranial injuries is based on this concept. The explanation given is that the blood cells, freed from the lacerated vessels by the trauma, plug and also, by compression from without on the pacchionian granulations and arachnoid villi, prevent totally or partially the escape of cerebrospinal fluid into the venous sinuses, and the resultant back pressure on the brain of the spinal fluid produces increased intracranial tension and cerebral edema. It is a plausible explanation and may be a factor in some cases, but it is unsatisfactory in many ways; it fails to explain the cases in which there is definite hypotension of the spinal fluid, as described by LeRiche, and also cases seen at operation in which the brain is shrunken and not swollen. Cassasa denied the existence of cerebral edema due to trauma, because of the fact that the convolutions are not flattened like those seen in edema of the brain following infection or associated with tumors. LeCount and Apfelbach described a "traumatic edema," and in a later article Apfelbach stated "that it is a generalized edema, and not a localized one about contusions." Rand<sup>21</sup> found edema in his fatal cases, and later Rand and Courville stated that "there is an actual increase in the amount of circulating fluid." They also found edema in the choroid plexus in a number of fatal cases. The actual increase in the amount of circulating fluid can be due to subarachnoid hemorrhage. Jefferson found a characteristic histologic picture of edema in patients who lived until the second or third day, and he observed "dry" and "wet" brains after injury. In unilateral subdural hemorrhage Vance observed a flattening of the brain on the side opposite the hemorrhage, and in bilateral hemorrhages with laceration of the brain flattening of the cerebral cortex was not prominent unless one side showed a large quantity of blood while the other contained a small amount. Vance also found edema at times, after from two to five days, adjacent to the laceration, and he stated that "no case in this series presented the degree of swelling that Apfelbach mentioned, and there was no example of death arising solely from this condition." From studies of lumbar pressure we are of the opinion that the chief increase in intracranial tension may be explained on the basis of hemorrhage with resultant displacement of fluid. We do not deny entirely the existence of cerebral edema in cases of injury to the brain, but we do say, with Jefferson, that if it does occur it is a late development. And we feel, further, that it is not a chief, or even an important, consideration in the treatment of these patients. Alcohol as an edema-producing factor in these cases has not as yet been studied.

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21. Rand, C. W., quoted by Rand and Courville.<sup>12</sup>

Unconsciousness or semiconsciousness was noted in 190 instances, or 54.4 per cent of our cases, as shown in table 4.

Unconsciousness was present in 61 of the 73 fatal cases, or 83.5 per cent, and 61 of the 190 unconscious patients died, or 32.1 per cent. Mental excitement was observed in many instances, and in some it was due to trauma plus alcohol. Traumatic delirium as described by Riddoch was also observed, but it was much less frequently noted than excitation. Alcoholism was the causative factor in some of the cases showing unconsciousness. In 12 fatal cases the patients were conscious on admission; death was caused in 5 by a terminal pneumonia, in 1 by meningitis, in 1 by epidural hemorrhage combined with laceration of the brain (this patient was operated on), in 1 by septicemia from a massive contusion of the back and in the remaining 4 by exhaustion. Most patients in the group with nonfatal fractures recovered from the unconsciousness within a few hours; in a few it lasted twenty-four hours, and in only 4 did it last as long as thirty-six hours.

TABLE 4.—Incidence of Unconsciousness and Semiconsciousness

	Class A		Class B			
	Cranio-cerebral Injuries		Group 1 Skull Fractures		Group 2 Intracranial Injuries	
	Lived	Died	Lived	Died	Lived	Died
Unconscious.....	24	19	17	22	19	6
Semiconscious.....	30	7	25	7	14	0
Conscious.....	45	4	56	6	44	2
Total.....	99	30	98	35	77	8

Cohen<sup>22</sup> in 1917 and Blakeslee<sup>23</sup> in 1929 reported on the findings in the eyes of patients with fractured skulls at Harlem Hospital. Blakeslee's report was especially comprehensive, and we studied many of the same patients on whom he made his observations. This series of cases was studied by us at a later time, and our findings confirmed his work. He reported a mortality of 95.5 per cent in patients showing bilateral widely dilated and fixed pupils, while it was 50 per cent in patients exhibiting a unilateral fixed pupil. Kearney<sup>24</sup> reported no change in the fundi during the first twelve hours after injury, but he reported changes in the fundi in 1 in 6 cases of severe injury after twelve hours. Papillitis occurred in our cases in few instances.

22. Cohen, Martin: The Value of Eye Manifestations Complicating Fractured Skulls, *Arch. Ophth.* 46:258, 1917.

23. Blakeslee, George Arthur: Eye Manifestations in Fracture of the Skull, *Arch. Ophth.* 2:566 (Nov.) 1929.

24. Kearney, J. A.: The Value of Eye Observations in Fracture of the Skull and Severe Head Injuries, *New York State J. Med.* 22:341 (Aug.) 1922.

McCreery and Berry pointed out the value of using the pupillary signs as an indication of the patient's progress. As a rule, a unilateral dilated fixed pupil occurs on the same side as the lesion, but in one of our cases we observed a dilated fixed pupil on the side opposite to the laceration of the brain.

In a recent case of combined epidural hemorrhage and laceration of the brain, the pupil on the side of the laceration was dilated and fixed, while the pupil on the side of the epidural hemorrhage was smaller and reacted to light. Blakeslee was especially careful to point out the variation in the pupillary status as it occurred in different cases and as it changed from time to time in the same patient.

The incidence of the usual objective signs of injury to the head is shown in table 5.

The lacerations, contusions and hematomas of the scalp varied in number, extent and degree, and were valuable at times in furnishing a clue as to the nature of the trauma and the direction of the force in

TABLE 5.—Incidence of Objective Signs of Injury

	Class A Cranio- cerebral Injuries	Class B		Total	
		Fractured Skulls	Intracranial Injuries	Number	Per Cent
Lacerations of scalp.....	26	55	24	105	30.2
Hematomas and contusions.....	22	28	27	77	22.1
Ecchymosis of eyelids.....	87	91	58	236	68.0
Bleeding from one or both ears.....	23	25	2	50	14.6
Bleeding from nose or mouth.....	27	15	17	59	14.3

relation to the head, which aided in localizing the lesion. Ecchymoses about the eyes were present in 68 per cent of these cases.

Bleeding from one or both ears is a rather reliable sign of fractured skull. Gurdjian<sup>25</sup> reported bleeding from the ears in 476 of 2,600 cases; his mortality in cases of unilateral bleeding from the ear was about 37.5 per cent, and in bilateral bleeding it was 67.3 per cent. Miller and Lauppe<sup>26</sup> reported mastoiditis as a sequel of fracture of the temporal bone in a case in which there was bleeding from the ear, and they found records of 22 similar cases; Gurdjian reported 3 cases in his series. Bleeding from the ear is not always due to a fracture of the skull, and this was true in 2 of our cases; in the first the bleeding was from a bleb on the wall of the external auditory canal, and in the second it was due to a simple rupture of the tympanic membrane. Vance cited a case in which the bleeding was from a laceration of the external auditory canal. The escape of spinal fluid from the ear makes

25. Gurdjian, E. S.: Ear Complications in Acute Craniocerebral Injuries, *Radiology* 18:74 (Jan.) 1932.

26. Miller, R. K., and Lauppe, F. A.: Mastoiditis Following Skull Fracture, *J. Michigan M. Soc.* 29:912 (Dec.) 1930.

the diagnosis of fracture of the skull certain, but in some instances the fluid is undetected owing to its admixture with blood.

The escape of cerebrospinal fluid from the ear was observed in 2 of our patients, both of whom died. Meningitis occasionally develops in cases of fracture involving the middle ear.

Bleeding from the nose and throat is of interest in that in unconscious patients some of the blood may flow into the trachea and bronchi and initiate pneumonia. It may also produce sounds in the trachea that simulate those of pulmonary edema. In 3 of our cases bleeding from the mouth was due to an associated fracture of the mandible.

The pulse rate varied so widely and was influenced by so many factors that we do not consider it a dependable guide. Many patients on admission showed a very rapid and feeble pulse owing to shock, and in many of the fatal cases the rapid pulse persisted until death. Bradycardia was of importance in some cases. It was present in 16 patients on admission; 13 of these patients died, while in the remaining 3 the pulse rate returned to normal within twenty-four hours. In 6

TABLE 6.—*Paralysis*

	Total Number of Cases	Nonfatal Cases	Fatal Cases
Cranial nerve paralysis.....	70	47	23
Facial nerve paralysis, alone.....	26	17	9
Hemiplegia .....	31	4	27
Monoplegia (exclusive of that of cranial nerve).....	10	3	7
Motor aphasia .....	1	1	0

patients bradycardia developed after four days, persisted for several days and then disappeared. The changes in the volume of the pulse and the rapidity with which they occurred impressed us more than did the changes in the pulse rate.

The temperature on admission of the patients who were in a state of shock was subnormal. All patients who were not in a state of shock showed an average temperature range of between 100 and 101 F. The temperature showed wide variation within a few hours, and in the fatal cases, even in the absence of infection, it rose sharply to 105 or 106 F. just before death. In practically all of the nonfatal cases, irrespective of the temperature on admission, the temperature ranged between 99 and 101 F. for several days, and then descended to normal.

The neurologic aspects of these cases were studied by Dr. George A. Blakeslee and his associates. The incidence of various forms of paralysis is shown in table 6.

Dementia paralytica was observed in all fatal cases just before death. Abnormal reflexes were observed in most of these cases, and varied according to the site of the lesion. Convulsions were observed in 22 patients, 18 of whom died.

Vomiting is frequently mentioned as a symptom, but it was observed only 11 times in this series; in a single instance the vomiting was projectile.

Rigidity of the neck in the absence of meningitis was noted in 11 cases, and some of these cases exhibited a suggestion of a Kernig sign. Russell<sup>27</sup> observed rigidity of the neck 38 times in 200 cases, and stated that "it is often a sign of subarachnoid hemorrhage." Vance said: "The occurrence of a rigid neck and a positive Kernig sign can be caused by a subarachnoid hemorrhage." Ohler and Hurwitz<sup>28</sup> observed stiffness of the neck in 19 of 22 patients whose condition was diagnosed as spontaneous subarachnoid hemorrhage. They found the Kernig sign frequently present. We do not deny that subarachnoid hemorrhage may produce nuchal rigidity, but it seems to us that in some of our cases it could be explained by concomitant injury of the muscles of the neck at the time of the original injury and in others by the way the assistant bent the neck while the spinal puncture was being done, especially if the patient strained at this time, in some cases thereby producing muscle strain with or without a sprain of the ligamentum nuchae. This is supported by the fact that 2 of our patients showed a clear spinal fluid, and many patients with fracture of the occipital bone failed to show rigidity of the neck.

Urinary incontinence occurred frequently in this series, and we deemed it a most important prognostic sign. During the early part of this work, its occurrence was not always recorded, and so it is impossible for us to present complete figures. We have observed it in more than 50 cases. We feel safe in saying, however, that it occurred in the great majority of fatal cases, and that its occurrence in a patient not under the influence of alcohol is of grave prognostic significance. The beds of these patients are wet, and there is never incontinence of feces. If urinary incontinence persists in an alcoholic patient after the influence of alcohol has worn off, this persistence is in our opinion indicative of severe cerebral injury. The postmortem observations in cases showing urinary incontinence were laceration of the brain and compression of the brain from subdural or extradural hemorrhages.

Associated injuries were present in 23 instances, as outlined in table 7.

Readings of blood pressure were made on every patient as soon after admission as possible. The highest systolic pressure recorded was 240 mm. of mercury, with a diastolic pressure of 110 mm., while the

27. Russell, Ritchie: Discussion on the Diagnosis and Treatment of Acute Head Injuries, *Proc. Roy. Soc. Med.* **25**:751 (March) 1932.

28. Ohler, W. R., and Hurwitz, David: Spontaneous Subarachnoid Hemorrhage, *J. A. M. A.* **98**:1856 (May 28) 1932.

lowest pressure was so low that it could not be read (in this patient the reading was zero for about thirty minutes, after which it rose to 70 mm. systolic and 40 mm. diastolic, and it remained at or about that level until the patient died three days later). In 54 fatal cases the systolic pressure was above 130 mm. of mercury, and averaged about 150 mm., while in 11 fatal cases the systolic pressure was below 90 mm. In fatal cases the blood pressure readings were either above or below normal. No patient that recovered exhibited a systolic pressure below 90 mm., and most of the patients with nonfatal cases were found to have a blood pressure that was normal or nearly so. The relationships between the gradual increase in intracranial pressure and the blood pressure are definitely known, but we are not satisfied that the variations in blood pressure and its relationships in cases of cerebral trauma are as simple as is generally believed. We have occasionally found the

TABLE 7.—*Associated Injuries in Addition to Fractured Skulls and Intracranial Injuries*

Fracture of:	Number of Cases	Number of Fatal Cases
Femur.....	4	3
Mandible.....	3	1
Humerus.....	3	1
Ribs.....	4	3
Vertebrae.....	2	2
Pelvis.....	1	0
Tibia and fibula.....	2	2
Metacarpals.....	1	1
Clavicle.....	1	0
Patella.....	1	0
Ruptured spleen.....	1	1
Massive contusion of back.....	1	1
Total.....	24	15 or 62.5%

same mechanism at work in these cases of trauma as in cases of tumor of the brain, but we feel in general that there are one or more added factors due to the trauma and also that there is insufficient time for the various compensatory and regulatory mechanisms of the cerebro-spinal and circulatory systems to get into play, as they undoubtedly do in cases of slow cerebral compression; therefore the process is extremely complicated and difficult to interpret, except in its obvious phases.

Diagnostic spinal taps are made as a routine on all patients immediately after their admission to the hospital. This procedure is simple and harmless when properly done, and we justify its routine use, after admitting that in an occasional case harm may result, on the grounds that in many cases acute craniocerebral injury would otherwise be undiagnosed and untreated. The Ayer water manometer is used for all pressure readings. We discarded the small mercury manometer after using it for several years, as it was not as accurate or reliable as the water manometer. Our findings are shown in table 8.

Jackson,<sup>29</sup> Sharpe,<sup>30</sup> Rodman,<sup>31</sup> Fay<sup>32</sup> and many other serious workers have stressed the value of determinations of spinal fluid pressure as a guide to treatment. In the average fatal case the intraspinal pressure was above normal; on the other hand, not infrequently we found hypotension. In a few cases readings were not made because of the death of the patient soon after admission to the hospital, and a few patients refused to have the determination made. It is unwise to place too much emphasis on lumbar pressure readings, owing to the fact that the rise and fall of intraspinal pressure often occur suddenly and without apparent cause; and, too, very slight changes produce marked variations in the readings, as for example, respiration and slight changes in position. Many cases in which injury was suspected and which later proved to be instances of alcoholism showed high pressure although there was no injury. In the absence of other obvious clinical signs, these readings have aided us little as regards prognosis.

TABLE 8.—*Spinal Fluid Pressure Readings*

Spinal Fluid Pressure Readings in Mm. of Water on Admission to Hospital	Class A		Class B			
	Craniocerebral Injuries		Group 1 Skull Fractures		Group 2 Intracranial Injuries	
	Lived	Died	Lived	Died	Lived	Died
0 to 50	1	3	10	4	4	2
50 to 120	57	6	32	2	31	2
120 to 200	23	9	38	6	15	2
200 to 300	11	3	7	5	14	1
300 to 500	2	2	4	5	4	1
500 to 700	0	3	1	5	1	0
Total	94	26	92	27	69	8

After the spinal fluid pressure reading is made, about 5 cc. of spinal fluid is collected separately in three test tubes, and the fluid in the third test tube is sent to the laboratory for a red and a white cell count. The red cell count is recorded on every patient's chart. We no longer speak of a "pink" or a "bloody" spinal fluid, but describe it in terms of the red cell count. This is done in the interest of greater accuracy. An opalescent spinal fluid was observed 8 times. Erythrocyte and leukocyte counts of the spinal fluid were made in 85 nonfatal and in 47 fatal cases of proved fractured skull. In the 85 nonfatal cases the average red cell count was 39,289, while the average white cell count

29. Jackson, Harry: *The Management of Acute Cranial Injuries by the Early, Exact Determination of Intracranial Pressure and Its Relief by Lumbar Drainage*, Surg., Gynec. & Obst. **34**:484 (April) 1922.

30. Sharpe, William: *Diagnosis and Treatment of Brain Injuries with and without Fracture of the Skull*, Philadelphia, J. B. Lippincott Company, 1920.

31. Rodman, J. Stewart: Editorial, Surg., Gynec. & Obst. **48**:437 (March) 1929; *Surgical Management of Cranial Injuries*, Ann. Surg. **92**:1017 (May) 1931.

32. Fay, Temple: *Head Injuries. The Results Obtained with Dehydration in Forty-Eight Consecutive Cases*, J. Iowa M. Soc. **20**:447 (Oct.) 1930.



was 653, and the average differential count was polymorphonuclear leukocytes 60 per cent and lymphocytes 37 per cent. The hemoglobin, according to the Sahli method, averaged 13 per cent. In the 47 fatal cases the red cell count averaged 857,813, the white cell count averaged 1,170, and the differential count averaged polymorphonuclear leukocytes 65 per cent and lymphocytes 34 per cent; the average hemoglobin was 21 per cent. It is seen that the more serious the injury, the higher was the red cell count, as well as the white cell count and the percentage of hemoglobin.

Urinalyses were made on 318 patients, and in many cases several examinations of the urine were made. Dextrose was found in the urine of 19 patients, and of these 19 patients 6 died, or 31.5 per cent. All patients that were conscious were allowed to void urine, while unconscious patients were catheterized. In cases of incontinence a urinal was adjusted to the penis to collect the urine. Determinations of blood sugar were made on 35 unconscious patients; the amount was above 120 mg. in 12 patients, or 31.4 per cent. Seven of the 12 cases exhibit-

TABLE 9.—*Erythrocyte and Leukocyte Counts in Cases of Fractured Skull*

	142 Nonfatal Cases	54 Fatal Cases
Red cell count, average.....	4,464,436	4,398,704
White cell count, average.....	9,548	12,957
Differential count, average		
Polymorphonuclears.....	75%	62%
Lymphocytes.....	24%	21%
Hemoglobin.....	81%	77%

ing hyperglycemia were fatal. The blood sugar level was normal or below normal in the remaining 23 cases. The blood for the determinations of blood sugar was taken immediately after the arrival of the patient in the ward. Our findings are, therefore, at variance with those of Mock and de Takats,<sup>33</sup> who stated that "head injuries of sufficient severity to cause unconsciousness result constantly in hyperglycemia." Their opinion is based on an experimental study and observations made in 10 clinical cases. Only 3 of the cases that showed hyperglycemia showed sugar in the urine. We made subsequent determinations of blood sugar at twenty-four hour intervals on the 12 hyperglycemic patients, and in only 2 instances did the blood sugar level remain above normal for over twenty-four hours.

Erythrocyte and leukocyte counts were made in 142 nonfatal cases of proved fracture of the skull and in 54 fatal cases of fractured skull. The average counts are shown in table 9.

The blood was examined within four hours after the patient's admission. Cases showing associated injuries were excluded from

33. Mock, Harry E., and de Takats, G.: Hyperglycemia Following Head Injuries, *Ann. Surg.* 90:190 (Aug.) 1929.

this group. There was a higher white cell count in the fatal cases, but our figures are not nearly as high as those obtained by Wright and Livingston.<sup>34</sup> Wright and Livingston have called attention to the diagnostic value of leukocytosis in intradural hemorrhage, and Moody<sup>35</sup> considered it of diagnostic value in extradural hemorrhage.

Roentgen examination is one of the most important examinations to be made in these cases. Our routine is to have roentgenograms made while the patient is in transit from the office of admission to the wards, unless he is in a state of very deep shock. Unconscious patients must be handled with extreme gentleness, and exposures made with rapidity by one skilled in taking roentgenograms of the skull. The diagnosis of fracture of the skull can be made in living persons with certainty only by means of roentgen examination, except in cases of penetrating wounds of the skull, which are usually compounded and depressed and in which one can see directly that the skull is fractured. Stereoscopic plates should be made in each case, and we advise the taking of views of the frontal and occipital and of the two lateral regions of the skull, making eight films in all. We do not try to get a roentgenogram of the base of the skull, because in our opinion it is dangerous. In our experience most basal fractures extend upward onto the lateral walls for a sufficient distance for them to be detected in an ordinary eight film study. Flat plate studies are practically worthless, as they do not give a proper concept of the fracture if one is found, and, too, it is impossible in many instances to differentiate suture lines and vessel markings from fractures. In fractures of the frontal sinus it is impossible to tell on a flat plate which wall of the sinus is fractured. We obtained roentgenograms showing evidence of fracture in 263 of the 347 cases, or 75 per cent. Stewart<sup>36</sup> reported a roentgenologic study of 300 cases of so-called "head injuries" from Harlem Hospital in 1925, in which 20 per cent of the cases showed evidence of fracture. Fay reported an incidence of 24.8 per cent of fractures proved by roentgen examination and seen at operation in a series of 189 cases.

In only 2 of our 35 fatal cases, in all of which autopsy was performed, did the autopsy disclose a fracture that we were unable to find on roentgen examination. We were able to make the diagnosis of combined epidural and subdural hemorrhage in 4 cases by means of roentgenologic study (the diagnosis of epidural hemorrhage was based on the fact that there was comminution of bone over the groove of the

34. Wright, Arthur M., and Livingston, Edward M.: The Leucocytosis of Internal Hemorrhage, *New York State J. Med.* **23**:286 (July) 1932.

35. Moody, W. B.: Fracture of Cranial Bones, with Especial Reference to Extradural Hemorrhage, *J. A. M. A.* **74**:511 (Feb. 26) 1920.

36. Stewart, William H.: Skull Fractures, New York, Paul B. Hoeber, Inc., 1925, p. 5.

middle meningeal artery). Three of these patients were operated on; 2 died and 1 lived. Autopsy in the 2 fatal cases in which operation had been performed and in the fatal case in which there had been no operation showed a large laceration of the brain complicating the extradural hemorrhage. Luckett<sup>37</sup> stated several years ago that symptomless fractures are relatively common after even apparently trivial violence, and urged the routine use of roentgen examination in all instances in which injury of this type is suspected. Encephalograms have been made in some of these cases, and we can testify to their value in giving information regarding permanent damage done by the trauma, as was first pointed out and demonstrated by Pancoast and Fay.<sup>38</sup> One of Grant's<sup>39</sup> cases of chronic subdural hematoma showed the value of roentgen examination in helping to make the diagnosis of this condition at times; we did not have any case of this kind in this series, however.

In line with the pioneer work of Connors, we used conservative nonoperative treatment. In the cases in which operation was not performed it consisted chiefly of rest in bed, good nursing and the maintenance of nutrition. Early in our work we used intravenous injections of hypertonic solution of dextrose in 20 seriously injured patients, 19 of whom died; we stopped using this treatment, as we are now of the opinion that the patients who live after receiving injections of dextrose would live without them, and in some instances it seemed to us that the injections hastened death. Death in these cases is due to cerebral compression from hemorrhage caused by laceration of the brain, and as dextrose cannot stop hemorrhage or heal a lacerated brain its use seems illogical.

Browder's<sup>40</sup> case demonstrates this point, and Jefferson has had the same experience in some of his cases. We agree that hypertonic solution of dextrose will shrink the brain, but this is a temporary effect, and the shrinkage that occurs allows space for more bleeding and a subsequently larger compressing mass. Recent experimental work on dogs by Milles and Hurwitz<sup>41</sup> showed that the reduction of intracranial pressure by single doses of hypertonic solutions of salt and dextrose

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37. Luckett, William H., in Stewart, William H.: *Skull Fractures*, New York, Paul B. Hoeber, Inc., 1925, p. 15.

38. Pancoast, H. K., and Fay, Temple: *Encephalography: Roentgenological and Clinical Considerations for Its Use*, *Am. J. Roentgenol.* **21**:421 (May) 1929; *Encephalography as the Roentgenologist Should Understand It*, *Radiology* **15**:173 (Aug.) 1930.

39. Grant, Francis C.: *Chronic Subdural Hematoma*, *Ann. Surg.* **86**:485 (Oct.) 1927.

40. Browder, Jefferson: *Dangers in the Use of Hypertonic Solutions in the Treatment of Brain Injuries*, *Am. J. Surg.* **8**:1213 (June) 1930.

41. Milles, George, and Hurwitz, Paul: *The Effect of Hypertonic Solutions on Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Toxicity*, *Arch. Surg.* **24**:591 (April) 1932.

is transient, and that a secondary rise in pressure follows which may occasion death. Weed and his co-workers' <sup>42</sup> original work was done on cats with normal brains, and not brains that had been subjected to severe trauma and compressed by blood clots. We can testify to the fact that in the human subject hypertonic dextrose solutions will produce an almost instantaneous shrinkage of the brain. This was seen during an operation on a patient who showed focal signs of pressure; when we opened the dura, the arachnoid seemed full of fluid and the brain bulged into the opening (at this time 50 cc. of a 50 per cent solution of dextrose was given intravenously, and immediately the brain shrank and its convex surface became concave, as if the ventricle on that side had suddenly emptied itself of fluid). Solutions of magnesium sulphate were not used in the rectum, because previous experience at this hospital had shown this treatment to be unsatisfactory.

Lumbar drainage was used in only 15 cases, and we do not advocate its use. In November, 1931, we used lumbar drainage combined with

TABLE 10.—Operations

Total number of cases.....	347
Total number of operations.....	15
Compound depressed fracture (1 death or 12.5%).....	8
Simple depressed fracture (no deaths).....	4
Combined epidural and subdural hemorrhage, dura not opened (3 deaths or 75%).....	4
Subdural hemorrhage with focal signs (2 deaths or 100%).....	4
Total number of deaths (33.5% mortality).....	6

limitation of the intake of fluid, as suggested by Fay, in 15 patients, and these patients seemed so much worse clinically than is usual that we discontinued the use of drainage and stopped limiting the intake of fluid. The idea has grown with us, since we have heard of so many permanent poor end-results in other clinics, that the drying of the brain and spinal cord and of the leptomeninges may, since it is unphysiologic, contribute no small amount to such an unsatisfactory end-result. We are trying to check as many of our end-results as possible by means of encephalograms. We have used phenobarbital and amytal with good results in allaying excitement due to cortical irritation. In 2 cases we

42. Weed, Lewis H., and McKibben, Paul S.: Pressure Changes in the Cerebrospinal Fluid Following Injection of Solutions of Various Concentrations, *Am. J. Physiol.* **43**:512, 1919. Weed, Lewis H., and Hughson, Walter: Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations with Reference to the Cerebrospinal Fluid, *ibid.* **58**:53, 1921; The Cerebrospinal Fluid in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container, *ibid.* **58**:85, 1921; Intracranial Venous Pressure and Cerebrospinal Fluid Pressure as Affected by Intravenous Injection of Various Concentrations, *ibid.* **58**:101, 1921.

have used avertin with good results. Patients in a state of shock are given fluids by mouth and by hypodermoclysis, the amount varying with each case.

The patient is kept warm at all times, and suction is used to keep the throat clear of blood and mucus. In unconscious patients nutrition is maintained by means of duodenal feedings and nutritive enemas. The bed is put in Fowler's position, and elderly patients are placed on an air mattress.

Operations were performed in all cases of compound depressed fractures, in some of simple depressed fractures, and in those with epidural or suspected epidural hemorrhage. No patients with fractures of the frontal sinus were operated on, although when we had a case in which we were certain that the dura was torn we operated and closed the dura, as suggested by Teachenor.<sup>43</sup> No operation was performed for cerebral compression, as it is our belief that if the patient lives he would have lived without operation. Eighteen operations were performed in this series, as shown in table 10.

#### CONCLUSIONS

1. This study confirms the work of others showing that the non-operative treatment of fractured skulls is the best treatment known today.

2. Much more intensive investigation is needed to lower still further the mortality in these cases.

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43. Teachenor, F. R.: Intracranial Complications of Fracture of the Skull Involving Frontal Sinus, *J. A. M. A.* **88**:987 (March 26) 1927.

# FIBROMYOMA OF THE UTERUS

REPORT OF A CASE OF A SIXTY-FIVE POUND SOLID FIBROMYOMA,  
WITH A REVIEW OF LARGE CYSTIC AND SOLID UTERINE MYOMAS

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My object in writing this paper is to place on record the operative removal of an exceptionally large myoma of the uterus, and at the same time to learn, if possible, from a review of similar cases, if anything further could have been done to promote a more successful result. I was also interested to see how this tumor compared in size with others reported in the literature and what the mortality in a series of such cases would be. Knowledge of mortality is very important, because the question always arises in the mind of both the patient and the surgeon whether it is worth while to attempt operation when the tumor has reached such huge proportions. I felt that I might pick up some details of technic, at operation, in preoperative or postoperative care, that might help me should a similar case present itself. Therefore, the literature on this subject was reviewed, as far as possible, back to the beginning of the period of aseptic surgery. I set 30 pounds (13.6 Kg.) as the arbitrary minimum weight limit of the tumors to be included in this series, and was able to collect over thirty cases that had complete enough records to make them valuable.

## REPORT OF A CASE

*History.*—Mrs. Dora C., aged 56, a housewife, was admitted to the service of Dr. T. S. Cullen at the Church Home and Infirmary, Baltimore, on Jan. 31, 1931. Her chief complaint was swelling of the abdomen of twenty years' duration. The family history was essentially unimportant. Her menstrual periods began at the age of 13, lasted from three to four days, were never painful or excessive in amount, and ceased completely nine years before the present admission. Since this time there had been no discharge of any sort and no pelvic pain. The patient had been very dyspneic on even the slightest exertion for as long as eight years and had been gradually getting worse in this respect as the tumor had enlarged. She had had to sleep on several pillows for some time, and lately had had to sit up at night. She had been constipated, but otherwise the gastro-intestinal system had been normal. There had been no urinary symptoms of any sort.

The present illness began twenty-one years ago, following an abortion; the patient's family doctor noticed that there was a small hard lump in the right lower quadrant of the abdomen. He felt that this was probably a tumor of the uterus and advised operation, but she refused to have anything done. The mass continued to grow, moving upward and outward. No pain or other discomfort was associ-

ated with its increase in size, until lately. As the mass increased in size and tension became greater on the abdominal wall, a small ventral hernia which had been present increased gradually to a very great size until it reached nearly to the patient's knees, hanging down like an inverted cone with the base uppermost. Four years ago, because of the weight and appearance of the tumor, the patient sought the advice of Dr. Cullen. He advised surgical removal, but she again refused operation. For the past two years she had been a semi-invalid because



Fig. 1.—Front view of Mrs. Dora C. to show position of the lobules of the tumor preoperatively.

of the weight of the tumor and shortness of breath. Three weeks ago she had a period when she suffered marked chills and fever, and the abdominal tissues over the most dependent portion of the tumor became very red and sore. Hospitalization was advised, and after much hesitancy the patient finally consented to be admitted.

*Physical Examination.*—The patient was well developed and nourished and was lying in bed on her right side, propped up with pillows to an angle of about 45 degrees. Her color was not very good, and respirations were rapid and rather

shallow. The general physical examination gave essentially negative results except for the cardiorespiratory system. There were slight enlargement of the heart, a few moist râles at the bases of both lungs and edema of the lower portion of the abdomen, legs and ankles. However, the respiratory rate was only 24 and the pulse rate, 90. The blood pressure was 100 systolic and 65 diastolic.

The abdomen presented the chief point of interest. There was a huge umbilical hernia which extended in a conical form 11 inches (27.9 cm.) below the symphysis pubis and was from 6 to 9 inches (15 to 22.8 cm.) in diameter. The walls of the abdomen and the hernia were very tense and showed dependent edema. The abdomen measured at the waist 55 inches (139.7 cm.), whereas normally the patient said her waist measured only from 32 to 34 inches (81 to 86 cm.). The abdomen was so tense and there was so much edema present that no good idea of the contents could be gained at this time. A little clear fluid was leaking from a point where a paracentesis had been made. Rectal examination gave negative

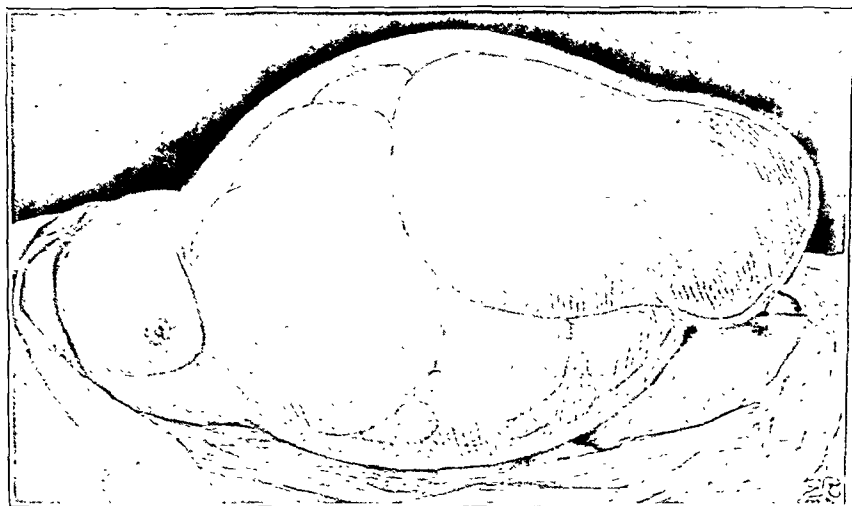


Fig. 2.—Lateral view of Mrs. Dora C. to show position of the lobules of the tumor preoperatively.

results. Pelvic examination showed relaxation of the outlet. Through the vagina no tumor mass could be made out because of the fluid present. It looked very much as if a large ovarian cyst with ascites was being dealt with.

On February 2, after more fluid had been drawn off and more leakage had occurred, a huge, irregular, hard mass could be felt filling the entire abdomen and also the large hernial sac. The tumor was clearly an unusually large fibroid and not an ovarian cyst.

After several days, during which time the patient was digitalized and hot compresses were applied to the area of induration of the abdominal wall until it had completely cleared up, operation was decided on, as the maximum preoperative improvement had been reached. The patient was clearly not a good risk, but something had to be done if any improvement could possibly be expected.

*Operation* (Dr. Cullen, February 7).—An elliptic incision was made, extending from one side to the other and embracing the hernia. The breadth of the ellipse was about 18 cm. The flap was gradually dissected free and the hernial ring exposed. It was 14 cm. across. The hernial sac contained a large myoma. When



the sac was opened still further, a second myomatous nodule appeared, then a third, and then a loop of large bowel which was adherent to the sac. Omental vessels ran into the surface of the tumor.

After the hernia was reduced and its contents freed, the large abdominal tumor was gradually delivered. There were five lobes in all. After the tumor was delivered, the vessels were tied from left to right; the left tube and ovary were not removed. It was difficult to get one's bearings. Down the right side was a lobule 12 cm. in diameter. It was situated in the broad ligament and was exceedingly difficult to enucleate. When the vessels were being clamped, a white cord was seen which appeared to be the right ureter and which finally proved to be this structure. How it was avoided, I do not know. The entire mass was removed, and all bleeding points were checked, but there was troublesome oozing in the broad ligament on the right side where the myoma had been shelled out. Two cigaret drains were left in this ligament and brought out through a right gridiron incision.

The appendix was tied up in adhesions and thickened; it was removed. The abdomen was then closed.

The patient stood the operation quite well until the last fifteen or twenty minutes, when her pulse became rapid and very weak. She received nearly 500 cc. of salt solution intravenously on the table and an infusion was also started. When she left the table her pulse was barely perceptible and could not be counted. Her color was poor, and she felt cold and clammy. The wound was dressed in the usual manner and a tight abdominal binder applied. No fluid was put into the abdomen.

*Postoperative Course.*—Following the operation the patient was temporarily moved into a side room still on the operating table, the head lowered, the body surrounded by hot water bottles and wrapped in warm blankets, and a transfusion of 500 cc. of citrated blood was given. During the succeeding twenty-four hours she received 1,000 cc. of coffee and saline by rectum in divided doses of 250 cc. each. Physiologic solution of sodium chloride by infusion and intravenously, 2,050 cc., 1 grain (0.065 Gm.) of morphine,  $\frac{3}{4}$  grain (0.048 Gm.) of ephedrine (hypodermically), 16 minims (1 cc.) of epinephrine (hypodermically), 58 grains (3.75 Gm.) of caffeine in doses of  $7\frac{1}{2}$  grains (0.49 Gm.) and 2 ampules of camphor in oil. At the end of this time she had failed to rally. Her pulse was 140, respirations, 24, and temperature, 101.6 F. On the following day, February 8, this same treatment was repeated together with another transfusion of 500 cc. of blood, but still the condition of shock persisted, and although the patient was conscious and talking rationally during most of this period, her condition gradually became worse, so that by midnight the temperature was 102.6 F.; the pulse rate, 140, and respirations, 44; she finally died at 2:35 a. m., February 9. It seems remarkable that in spite of all our efforts we were never able to overcome the condition of shock which set in during the last few minutes of operation, although the patient lived nearly forty-eight hours. Permission for complete autopsy was obtained, but did not show anything more than we already knew, as all the organs seemed entirely normal except for slight enlargement of the heart and a little edema at the bases of the lungs.

*Gross Description of the Tumor* (Dr. Norwood).—The specimen was that of a huge lobulated fibromyoma of uterine origin. It measured 30 by 60 cm. and weighed 65 pounds (29.5 Kg.). There were no areas of degeneration on the cut surface. No structure could be definitely identified as being uterine or ovarian tissue. One flattened out structure on the anterior surface of the tumor looked like a tube.

*Microscopic Examination.*—Examination under the microscope showed perfectly uniform typical fibromyomatous tissue with no degenerative changes.

A comprehensive analysis of the foregoing cases is not possible because of the many factors involved, but when one looks over the list superficially certain things stand out. Evidence of severe involvement of the cardiovascular system of the patients preoperatively, such as dyspnea, orthopnea, enlargement of the heart and edema at the bases of the lung, has usually been an indication that the patient would not

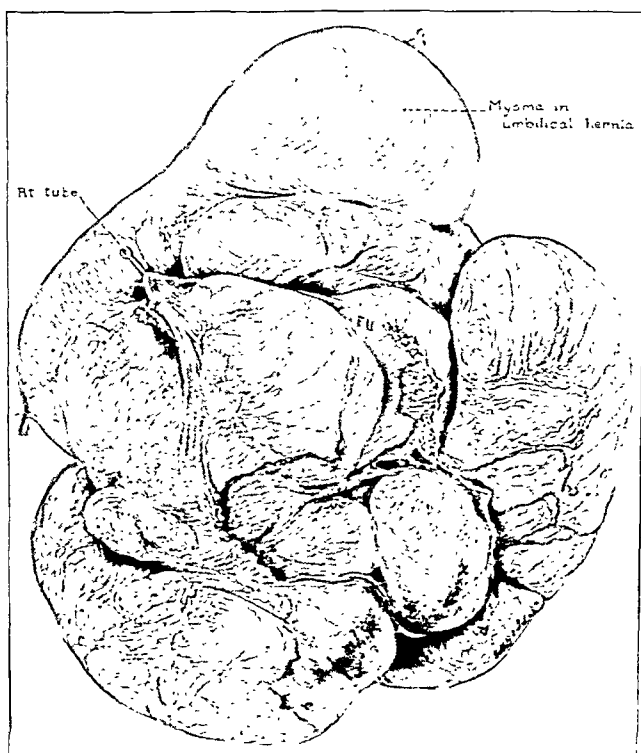


Fig. 3.—Specimen immediately after operation.

survive operation. The time consumed at operation and the fact as to whether the release of abdominal pressure was counteracted by external means or by the use of intra-abdominal fluid, such as physiologic solution of sodium chloride, have also been two indicators of the outcome, for in those cases in which operation was performed quickly and in which fluid was used in preference to external pressure, the mortality rate has been lower. The consumption of less time and the use of intra-abdominal fluid might have given our patient a better chance, whereas the fact that she had cardiac enlargement, edema at the bases of the lungs and severe dyspnea with rapid pulse on the slightest exertion

# *Review of Cases from the Literature*

Author and Date	Age of Patient	Duration of Symptoms	Condition of Patient Before Operation	Duration of Operation	Weight and Character of Tumor	Fluids Given at Operation	Result
Wells, T. S.: Brit. M. J. 1: 674, 1878..	36	10 yrs.	Good except for edema of legs and feet during menses	1 hour	68 lbs., 6 oz.; solid fibromyoma	None	Excellent recovery
Tait: Diseases of Women and Abdominal Surgery, ed. 2, New York, William Wood & Company, 1879, vol. 1, p. 187	63	26 yrs. (?)	Dyspnea; weight interfered with work as midwife	?	26½ lbs.;* solid fibromyoma	.....	Uneventful recovery
Dudley, F. C.: New York M. J. 39: 687, 1884	47	5 yrs.	Poor, cardiac weakness; emaciation; anemia	?	35 lbs.; solid fibroid	None	Hectic course; recovery
Stockard, C. C.: M. Rec. 26: 177, 1884	54	13 yrs.	Poor, emaciation; cardiac distress	No operation	135 lbs. (?) ; cystic fibroid	.....	Died 6 days after tapping
Thornton, K.: Lancet 1: 672, 1887....	56	5 yrs.+	General condition fair; details not given	?	30½ lbs. (approx. 5 lbs. fluid); solid fibroid	None	Slow but complete recovery
Pantock; M. Press & Circ. 46: 645, 1888	..	10 yrs.	Cardiac distress and albuminuria	Not given	64 lbs.; solid fibroid	.....	Died 6 days after operation; kidney failure (?)
Hunt, S. H.: Am. J. Obst. 21: 62 1888	53	21 yrs.	.....	Removed at autopsy	140 lbs.; fibroid with many cysts	.....	Good recovery
Werder, X. O.: New Orleans M. & S. J. 17: 247, 1889-1890	23	8 mos. (?)	Good	?	40 lbs. (estimated); fibrocystic	None	Died 5 days after operation; septicemia
McIntyre; St. Louis M. & S. J. 60: 137, 1891	38	?	Respiratory and cardiac distress	?	99½ lbs.; solid fibromyoma	.....	Good recovery
Doran, A.: Med.-Chir. Tr., London, 76: 323, 1892-1893	..	.....	.....	?	42½ lbs.; fibrocystic	.....	Recovery (?)
Eastman, J.: North American Pract. 5: 387, 1893	..	.....	.....	?	60 lbs.; solid fibroid	.....	Good recovery
Dalziel; Glasgow M. J. 41: 229, 1894...	38	1 yr. (?)	Good	?	33 lbs.; cystic myoma; 13 lbs. fluid	.....	Died from shock 4 hours after operation
Penrose, C. B.: Am. J. Obst. 35: 106, 1897	39	16 yrs.	Cardiac and respiratory difficulty for 4 years	45 minutes	87 lbs.; solid fibroid (edematous)	.....	Result not given
Ricketts; Cincinnati Lancet-Olin. 41: 331, 1898	52	4 yrs. (?)	Not given	58 minutes	65 lbs.; solid myoma	None	Died of shock during night
Gwinard; Bull. et mém. Soc. de chirurgiens de Paris 28: 201, 1902	40	23 yrs.	Good, except bedridden by weight	45 minutes	72½ lbs.; solid myoma	.....	Uneventful recovery
Madden, F. C.: Brit. M. J. 1: 70, 1902	28	2 yrs.+	Good	?	53 lbs.; soft, fleshy myoma	Filled abdomen with saline solution before closure	

Webster, J. C.: J. Obst. & Gynec. Brit. Emp. 4: 135, 1903	41	10 yrs.	Some dyspnea, otherwise good; 55 per cent hemoglobin	2.5 hours	87 lbs.; fibrocystic	Filled abdomen with saline solution before closure	Uneventful recovery
Brown: Lancet 1: 563, 1901	51	22 yrs.	Good until 3 weeks before death	None	70 lbs.; solid fibroid	.....	Tumor removed post mortem
Souligoux: Bull. et mém. Soc. de chir. urinaires de Paris 33: 1053, 1907	..	.....	.....	?	74 lbs.; cystic, 25 liters of fluid	.....	Recovery
Cullen, T. S.: J. A. M. A. 48: 1401 (May 1) 1907	53	20 yrs.	Edema of abdomen and legs; could not lie down because of weight of tumor	55 minutes	80 lbs.; cystic myoma	No note as to fluid	Good recovery; lived nearly 20 years
Packard, H.: New England M. Gaz. 43: 255, 1908	..	.....	.....	?	41 lbs.; solid myoma	.....	Recovery
Cullen, T. S., in Kelly and Cullen: Myomata of the Uterus, Philadelphia, W. B. Saunders Company, 1900, p. 118	18	4 yrs.	Good	?	39 lbs.; multicystic myoma resembling multi-ocular ovarian cyst	Some free fluid	Recovery
Coeran, H. S.: New Orleans M. & S. J. 43: 591, 1910-1911	48	8 yrs. (?)	Bedridden by weight, but otherwise good	?	95 lbs.; solid myoma	.....	Uneventful recovery
Pakowski: Bull. et mém. Soc. anal. de Paris 87: 375, 1912	..	.....	Good	.....	39 lbs.; solid myoma	.....	Uneventful recovery
Berry, C. C.: Indian M. Gaz. 48: 310, 1903	41	18 yrs.	Good except for dyspnea	?	40 lbs.; myoma with small cysts	1,000 cc. saline sol. while on table; none in abdomen	Uneventful recovery
Jones, E. L.: U. S. Nav. M. Bull. 45: 58, 1921	65	20 yrs.	Good	?	31 lbs.; cystic tumor (may be ovarian, no microscopic report)	.....	Uneventful recovery
Farmer, C.: Kentucky M. J. 24: 513, 1923	..	.....	.....	?	39 lbs.; fibromyoma	.....	Uneventful recovery
Parkinson, W. R.: Brit. M. J. 2: 1055, 1924	30	8 yrs.	Good	?	33 lbs.; soft fibromyoma	None	Good recovery
Stevens, T. G.: J. Obst. & Gynec. Brit. Emp. 32: 729, 1925	59	20 yrs.	Dyspnea; edema of legs	35 minutes	47 lbs.; solid myoma	None, but tight abdominal bladder used	Good recovery
Hicks, E. S.: Canad. M. A. J. 18: 59, 1928	..	.....	Good	1 hour +	65 lbs.; solid myoma	3 gal. of sterile water in abdominal cavity before closure	Good recovery; left hospital in 20 days
Grleich, C. O.: Zentralbl. f. Gynäk. 53: 1652, 1929	48	20 yrs.	Good	?	33 lbs.; solid myoma	.....	Good recovery
Peltrac, M.: Ann. J. Obst. & Gynec. 20: 669, 1929	35	.....	Good, except bedridden because of weight	?	133 lbs.; myoma with many small cysts	300 cc. of clotted blood on table	Died of pneumonia in 48 hours (?)

\* The tumor weighed 20½ pounds (12 Kk.) after standing twenty-four hours, yet the author calculated it to have weighed 68 pounds (30.8 Kg.) at time of removal, which does not seem reasonable.

† The author removed 71 pounds (32.2 Kg.) of fluid from the cyst by tapping six days previous to the death of the patient, but he added this to the postmortem weight for the total of 135 pounds (61.2 Kg.). For this reason the tumor probably weighed considerably less than he calculated.

would suggest that following the general rule the chances for a favorable outcome were poor from the beginning.

The mortality rate of the entire series is 21.4 per cent when the tumors removed post mortem and those cases in which the outcome was uncertain are excluded. To me this seems surprisingly low, considering the size of the tumors, the age of the patients and their general condition. This low mortality rate certainly indicates that the surgeon is entirely justified in urging operation on patients of this type, for the outcome if operation is not performed is certain death, whereas operation promises a favorable result in a high percentage of cases.

When the tumor in the case reported here is compared to the others of the same type (solid fibromyoma), it is found that six others have been reported that were larger (Wells, 1878, 68½ pounds [31 Kg.]; McIntyre, 1891, 93½ pounds [42.4 Kg.]; Penrose, 1897, 87 pounds [39.5 Kg.]; Gwinard, 1902, 72¾ pounds [33 Kg.]; Brown, 1904, 70 pounds [31.8 Kg.]; Cocram, 1910, 95 pounds [43.1 Kg.]. In these cases three of the patients made an uneventful recovery and three died. Two more cases are reported in which the tumors were of exactly the same weight (Ricketts, 1898, and Hicks, 1928), in both of which the patients made an uneventful recovery. This review did not show me anything more than that which is common knowledge in regard to the preoperative and postoperative care in these cases.

# DOUBLE GALLBLADDER

## REPORT OF A CASE

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AND

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Before the advent of cholecystography, clinical recognition of anomalies of the gallbladder was rarely recorded. Boyden<sup>1</sup> reviewed the subject of accessory gallbladder in 1926. His figures are based on the study of 10,000 domestic animals and 19,000 human beings. He found that this anomaly occurred once in every 8 cats, 28 calves, 85 sheep and 198 pigs and only once in from 3,000 to 4,000 human beings. Only 20 cases in human beings were recorded from 1674 to 1926. Boyden classified these into (1) vesica divisa, or bilateral gallbladder, and (2) vesica duplex, which was subdivided into: (a) Y-shaped, with two cystic ducts merging into one, and (b) ductular, with two complete cystic ducts opening separately into the common duct.

There were only 4 examples of the ductular variety in his series of 20 cases. Since the time of Boyden's publication, several more cases of this anomaly have been recorded. Priesel,<sup>2</sup> in 1927, reported a case and reviewed the older literature. Other cases of the ductular variety have been reported by Garofalo,<sup>3</sup> Braun,<sup>4</sup> Wolfson<sup>5</sup> and Holderman.<sup>6</sup> Wischnewsky<sup>7</sup> reported a case of the vesica divisa variety and Wakeley<sup>8</sup> a case in which there was apparently a Y-shaped bladder with two cystic ducts merging into one.

1. Boyden, E. A.: Accessory Gall-Bladder, *Am. J. Anat.* **38**:177, 1926.
2. Priesel, A.: Verdoppelung der Gallenblase beim Menschen, *Virchows Arch. f. path. Anat.* **265**:76, 1927.
3. Garofalo, F.: A Case of Double Gall-Bladder, *Bull. d. sc. med. Bologna* **5**:380, 1927.
4. Braun, A.: Doppelbildung der Gallenblase, *Zentralbl. f. Chir.* **53**:1055, 1926.
5. Wolfson, W. L.: Supernumerary Gall-Bladder, *Am. J. Surg.* **6**:88, 1929.
6. Holderman, H. H.: Double Gall-Bladder, *Ann. Surg.* **91**:475, 1930.
7. Wischnewsky, A. W.: Doppelgallenblase während der Operation aufgedeckt, *Arch. f. klin. Chir.* **135**:779, 1925.
8. Wakeley, C. P. G.: A Double Gall-Bladder Removed by Operation, *Brit. J. Surg.* **15**:334, 1927.

Besides these anatomically described cases, 5 cases of double gall-bladder have been reported by Nichols,<sup>9</sup> Climan,<sup>10</sup> Hayes<sup>11</sup> and Cave,<sup>12</sup> in which the diagnosis was made by cholecystography. These cases were apparently of the ductular variety, but only in Nichols' case was the organ removed surgically. The undoubted number of such cases since Boyden's summary, therefore, is 6 or, including his 4 cases, a total of 10. The other 4 cases discovered by means of cholecystography may or may not belong in this classification. We are adding another case to the list, in which the double gallbladder with two complete cystic ducts was removed surgically.

This anomaly is best explained by the formation of two embryonic buds from the common bile duct, instead of the usual one. These buds are originally solid cords of epithelial cells which later acquire a lumen.

#### REPORT OF A CASE

*History.*—A white woman, aged, 42, married, Jewish, had an irrelevant family history. A sister had died of tuberculosis in 1918. The patient was married at the age of 19 years; the husband and 4 children were living and well. A child had died of Pott's disease at the age of 3 years, probably contracted from the aunt. An abortion had occurred after the third pregnancy. The chief complaint was epigastric distress, jaundice and pruritus.

The patient attributed her present condition to two factors: 1. Four months before we saw her, she was dined and wined excessively on a trip to the east. No unusual digestive disturbances occurred at the time. 2. Two months before we saw her, she was in an automobile collision. There were no definite injuries, but she was badly shaken up and spent two weeks in the hospital. During this time, she had an attack of severe cramping pain in the epigastrium, with radiation around the right costal margin and through to the back. There was residual soreness. She then had repeated similar attacks, which usually followed automobile trips, but sometimes occurred at night. She belched frequently, was afraid to eat, and sometimes induced vomiting to obtain relief. Jaundice began three weeks before she consulted us, and had persisted. Intense general pruritus had annoyed her for over two weeks.

She had had an attack of similar pain followed by jaundice two and one-half years previously. Since that time she had been unable to eat veal and pickles. There had been minor attacks of indigestion but no real pain until the present illness. During her pregnancies she was troubled with heartburn but did not have serious difficulty.

The patient had had measles and pertussis in childhood. She had had tonsillitis frequently previous to tonsillectomy in 1915. Influenza, in 1918, was followed by inflammatory rheumatism. Operative repair of a rectocele was done in 1929.

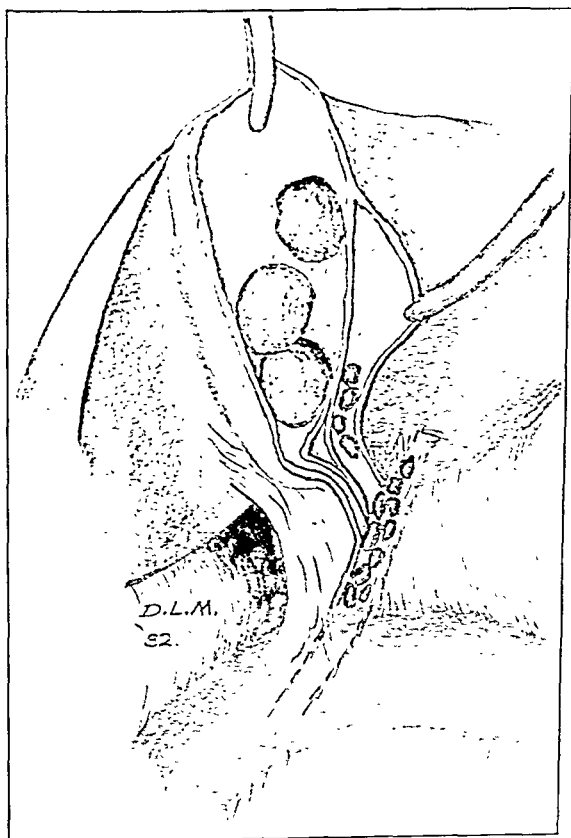
9. Nichols, B. H.: Double Gall-Bladder, *Radiology* **6**:255, 1926.

10. Climan, M.: Duplication of Gall-Bladder Demonstrated by Cholecystography, *M. J. & Rec.* **130**:73, 1929.

11. Hayes, R.: Double Gall-Bladder with Double Cystic Duct, *Radiology* **16**:56, 1931.

12. Cave, P.: Two Cases of Double Gall-Bladder, *Lancet* **1**:751, 1931.

*Physical Examination.*—Examination revealed a deeply jaundiced, obese woman, whose height was 63 inches (190 cm.) and whose weight was 176 pounds (79.8 Kg.); her usual weight was 190 pounds (86.2 Kg.). The temperature was 98.2 F.; the pulse rate, 100; the respiratory rate, 20, and the blood pressure, 130 systolic and 90 diastolic. The skin and sclerae were yellow. There were many scratchmarks all over the body. Examination of the head showed no abnormality, except a moderately coated tongue. A roll of fat lay just above the clavicle. The thyroid was not palpable. The patient did not present adenopathy. The breasts were



Diagrammatic sketch showing the conditions found at operation in a case of double gallbladder of the ductular variety.

large; no lumps or tenderness was present. There were normal expansion and resonance of the chest. The heart and lungs were normal. Percussion tenderness below the right scapula was noted. There was deep tenderness in the right hypochondrium. No masses or rigidity of the abdomen was observed. The edge of the liver was not palpable. The perineum was competent. The vagina was normal and the cervix short and small. There was a normal, movable uterus. No masses were found. A large, external hemorrhoid protruded posteriorly from the anus. The extremities and the tendon reflexes were normal.

*Laboratory Data.*—The urine was dark because of the presence of bile. The specific gravity was 1.016. Urinalysis showed: reaction acid, albumin; sugar.



none; pus, +; granular casts, 1. Examination of the blood showed: hemoglobin, 78 per cent (13 Gm.); red cells, 4,410,000; white cells, 10,200, with polymorphonuclears, 64; lymphocytes, 29; transitionals, 4, and eosinophils, 3. The serum bilirubin was 14.7 mg. and 13.62 mg.

Duodenal drainage showed only a faint bile stain after the injection of magnesium sulphate. The coagulation time was eight minutes.

A roentgenogram, without the use of dye, did not show stones. The diagnosis was chronic cholecystitis with stone in the common duct.

*Operation and Course.*—During five days in the hospital, 1 drachm of calcium gluconate was given three times a day. A diet high in carbohydrate and plenty of fluids were ordered. An intravenous injection of 500 cc. of a 10 per cent solution of dextrose was given twice daily on the two days before operation.

On Aug. 13, 1932, the patient was operated on at the Tacoma General Hospital. With the patient under spinal anesthesia, a long, oblique skin incision was made from the xiphoid to the right of the umbilicus. The fascia was divided in the same line, and the right rectus muscle was retracted laterally. The peritoneum was incised, and the intestines packed away to expose the gallbladder. The gallbladder was enlarged (grade 2) and thick-walled, and contained several stones. It was seized with curved forceps, and the peritoneal bands connecting it with the duodenum were snipped with scissors. Two gauze packs were placed, and exposure of the common duct was obtained by retracting the duodenum medially. The common duct was enlarged to about 2 cm. diameter. Several stones could be palpated in it. It was seized with two Allis forceps and incised longitudinally for about 1.5 cm. Much bile escaped, which was taken care of with a suction apparatus. Ten faceted, amber-colored stones were removed with a scoop, and a probe was passed through the papilla into the duodenum. Exploration of the hepatic ducts gave negative results. A Mayo Robson no. 18 catheter was placed to reach up into the right hepatic duct, and the incision in the common duct was closed with two layers of chromic 00 sutures. The catheter was transfixed with one of these and tied into place. The gallbladder was now removed by first exposing the cystic duct, which appeared enlarged tremendously, that is, to about the size of a thumb. It was divided between clamps. The cystic artery was then located, clamped and cut. The gallbladder mass was then peeled out of its fossa. The cystic artery was ligated separately. The large cystic duct stump was closed with two layers of 00 chromic sutures. At the time it was not recognized that we were dealing with two cystic ducts, instead of one, but the structure was too wide for simple ligation. The gallbladder fossa was covered by suturing peritoneal flaps at the edges. A strip of iodoform gauze was placed next to the gallbladder fossa, and this was covered with a plain Penrose drain. A Penrose cigaret drain was placed in Morrison's pouch. The appendix was seen to be obliterated. It was not disturbed. The wound was closed in the usual manner, bringing the drains out at the lower end of the incision. The immediate postoperative condition was excellent.

The convalescence was interrupted by severe and alarming hemorrhage on the ninth day, apparently secondary to infection of the wound. There was general persistent oozing from the fatty subcutaneous layer of the wound. After transfusion, the wound was opened in its entire length to clear out pus and blood. Gauze packing soaked in an extract of blood platelets controlled the bleeding. The patient left the hospital at the end of four weeks. She has regained normal health and strength.

*Pathologic Report (Dr. Martin).*—The unopened gallbladder measured 8 cm. in length by 4 cm. in the greatest diameter, which was the distance from the area of the attachment to the liver to the opposite surface. It was only on section that the roughly ovoid organ was found to contain two separate cavities of unequal length and diameter, both surrounded by a common, fascial coat, and each with a duct separated from the other throughout its course in the specimen.

The larger of the two cavities measured 8 cm. in length by 7 cm. in circumference, and contained three dark, smooth, stones moderately faceted, measuring 3 cm. across. The short cystic duct leading from this cavity was slightly tortuous, and had a diameter of 2 or 3 mm. The smaller cavity measured 5 cm. in length and 4 cm. in circumference, and contained four small, dark, heavily-faceted concretions, varying in greatest diameter from 5 to 12 mm. The cystic duct from the smaller cavity was straight and large, measuring 1 cm. in diameter. The walls of both cavities were moderately thick, that of the smaller cavity being appreciably thicker than that of the larger. The gross appearance of the mucosa was that of a normal-appearing trabeculation slightly accentuated in the smaller cavity.

In addition to the gallbladder there were ten small, dark, smooth heavily-faceted stones similar in size and appearance to those seen within the smaller cavity.

Microscopic sections from the wall of the larger cavity of the gallbladder showed well developed villi covered by columnar epithelium and many glandlike projections beneath the mucosa, some extending among the muscle bundles of the muscular layer. Cellular infiltration of the mucosa was moderate and diffuse, and was most conspicuous about the deeply-penetrating glands among the muscle bundles. The muscular coat was about twice the normal thickness, and showed a diffuse, cellular infiltration among which were a few pus cells.

Sections from the wall of the smaller cavity showed a similar picture, the differences being less conspicuous mucosal villi, milder and more superficial, glandular invasion, a thicker muscular coat and a greater tendency toward perivascular, focal infiltration of lymphocytes, plasma cells and endothelial leukocytes.

It is my belief that this was a true, double gallbladder having its origin in two ductal anlagen producing ducts of greatly unequal size and two mucus-lined cavities surrounded by a common fascial coat, though each had its own muscular investment. Judging, also, by color, shape and size, it seems most probable that the stones found in the common duct were formed in the smaller cavity, from which they easily escaped through the unusually large cystic duct leading from it.

The accompanying diagrammatic sketch is self-explanatory. It shows the conditions found in this case of true double gallbladder of the ductular variety.

## PYLEPHLEBITIS

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In the three and one-half year period from July 1, 1928, to Dec. 31, 1931, 4 cases of pylephlebitis were encountered at operation. Of this number, 3 were found as complications of 1,027 cases of acute appendicitis and 1 of 112 cases of acute cholecystitis. Although relatively uncommon, the dread results make this a formidable complication of acute intra-abdominal visceral disease.

Pylephlebitis may be developed in three ways: (*a*) by direct introduction of organisms into the lumens of vessels emptying into the portal vein; (*b*) by continuity from continuous organs when pyogenic organisms pass through the vessels from without, causing first phlebitis and then thrombosis; (*c*) in infections of the blood stream in which collections of micro-organisms that pass through other capillaries may settle in the liver because of the retardation of the blood stream where they multiply and then reach the portal vein and cause thrombophlebitis.

In this article we are concerned entirely with the pylephlebitis arising from the direct introduction of organisms into the lumens of vessels which empty into the portal vein, the focus of infection being either the appendix or the gallbladder. In such instances, the portal vein is found to be thrombosed and suppurative, the branches being dilated and filled either with pus or with brownish-green or greenish-black thrombus, and the periportal tissue is infiltrated with yellowish-green or slate-blue pus. The surface of the liver may show numerous small, light spots, and only after section can the relationship of these suppurative areas to the portal system be recognized. On the surface of the liver there may also be clay-colored necrotic foci and dark areas of congestion. The abscesses which develop around the portal vein spread and follow the branches of the vein, and early in the disease the hepatic lobules can still be recognized. Subsequently, however, the hepatic cells become completely destroyed, and larger coalescent abscesses occur. These lobular abscesses become confluent, and a cavity system develops, with many bulgings filled with thick pus which may have a fetid odor. The contiguous tissue frequently shows a grayish-green discoloration. The pathologic picture of the disease will be more completely described in the report of the individual cases.

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From the Koster Clinic, Crown Heights Hospital.

## REPORT OF CASES

CASE 1.—*History*.—C. F., a man, aged 45, was admitted to the hospital on Jan. 20, 1929, complaining of pain in the upper portion of his abdomen, fever and chills.

On January 2, the patient complained of a chilly feeling followed later by pain in the lower right side of the chest. He remained in bed for two weeks, during which time he was treated for pleurisy. His condition steadily grew worse, and he was taken to the hospital.

*Examination*.—This revealed a thin, undernourished, emaciated, white man, about 45 years of age, who looked acutely ill and lay in bed with his knees drawn up to his abdomen. Examination of the chest revealed a lagging on the right side, with flatness from the level of the fourth rib downward to the base posteriorly, and from the sixth rib downward anteriorly. The breath sounds were distant over this area of flatness. No râles were heard. The heart sounds were irregular in rate and rhythm; the aortic second sounds were diminished; no murmurs were heard. The apex beat was not displaced, and the heart percussed out within normal limits. There were tenderness and rigidity over the entire right side of the abdomen, but these were especially marked over the upper portion. Pressure release tenderness was referred to a point on the right side 1 inch (2.5 cm.) above and 2 inches (5 cm.) to the right of the umbilicus. No fluid was demonstrable. The spleen was palpable. The liver could not be palpated because of the rigidity, but on percussion the dullness of the liver extended downward about 4 fingerbreadths below the right costal margin. On admission, the temperature was 100 F.; the pulse rate, 124; the respiratory rate, 24, and the blood pressure, 80 systolic and 58 diastolic. Urinalysis revealed 3 plus albumin, no sugar, a few granular casts, a moderate number of pus cells and a few red cells. The hemoglobin was 70 per cent; the red blood cells numbered 3,850,000; the white blood cells, 12,100; there were 82 per cent polymorphonuclears, and 18 per cent lymphocytes.

A diagnosis of abscess of the liver was made.

*Treatment and Course*.—With the patient under spinal anesthesia, an aspirating needle was inserted into the subphrenic space, and pus was withdrawn. With the needle in situ, an incision was made parallel to the tenth rib on the anterior lateral surface of the lower right side of the chest. About 3 inches (7.6 cm.) of the rib was resected. The diaphragm was first sewn to the pleura in a circumferential direction around the point where the needle was inserted in order to wall off the area to be drained from the pleural cavity. The diaphragm was incised alongside the needle into the abscess cavity. The superior surface of the liver was adherent to the diaphragm all around this area. The abscessed area was about  $2\frac{1}{2}$  inches (6.27 cm.) in diameter and was situated on the superior surface of the liver and extended about 2 inches (5 cm.) into the substance of the liver. A gauze pack was placed all around the cavity, and a cigaret drain was inserted into the cavity after a specimen of the pus was taken for examination and culture.

The patient was given dextrose intravenously and saline by clysis. The pulse was weak and irregular. Stimulation was given, and he rallied somewhat. The next morning the patient had pulmonary edema, which progressed rapidly. The pulse became imperceptible, and the patient died soon afterward.

*Postmortem Observations*.—The abdomen contained a moderate amount of serohemorrhagic fluid. The appendix was bound down retroceally and showed evidence of an acute suppurative inflammation with an abscess in the meso-appendix, all of which was covered by omentum and walled off from the general

peritoneal cavity. The gastro-intestinal tract otherwise appeared normal. There was a thrombosis of the portal vein which on being incised exuded pus. The liver presented multiple abscesses varying in size from that of a pinhead to a large abscess cavity near the superior surface about the size of a plum. The spleen was enlarged about three times its normal size and was soft and spongy. The pancreas was normal. There was no thrombosis of the splenic or the pancreatic veins. The kidneys were normal. On cross-section, the liver showed many abscesses involving the branches of the portal vein. This case was typical of a suppurative pylephlebitis following appendicitis.

A culture of the pus showed gram-negative and gram-positive diplococci.

**Microscopic Appearance:** The wall of the portal vein was thickened, and its regular structure was replaced by granulation tissue, only a few distorted elastic



Fig. 1.—Low power magnification of a branch of the portal vein. The vein is filled with thrombus masses. The periportal connective tissue and its ramification to the adjacent hepatic tissue show cellular infiltration and edema.

fibers being left over. There was a well adherent thrombus, but parts of the thrombus were replaced by pure pus. The periportal fields throughout the liver showed considerable newly formed fibrous tissue. The walls of most of the veins were not recognizable. They were substituted by granulation tissue infiltrated with polymorphonuclears, while the lumens contained pus or necrotic masses. In the latter, huge bacterial aggregations were visualized. The hepatic tissue itself showed wide sinuses, many of which were filled with pus cells. Some foci of necrosis were seen from which the purulent infiltration seemed to radiate in all directions.

A noteworthy feature was the involvement of the lymphatics in the periportal tissue. There were numerous, considerably distended lymph vessels, some with apparently empty lumens and others filled with pus. Some of the latter showed circumscribed necrosis of their walls.

The microscopic appearance justifies the diagnosis of a subacute purulent pylephlebitis with periphlebitic lymphangitis.

*CASE 2.—History.*—A. D., a woman, aged 31, was admitted to the hospital on Aug. 28, 1931, complaining of pain in the abdomen, nausea, vomiting and general weakness. About three weeks prior to admission she had had generalized abdominal cramps accompanied by nausea and vomiting. This continued for several days, and at the end of a week the attack completely subsided, except that the patient felt weak. A few days prior to admission pains in the abdomen began again and were accompanied by nausea and chills.

The past history was irrelevant. The patient began to menstruate at 14 years of age; menstruation occurred every twenty-eight days and lasted four days. She had been married seven years. She had had no children, abortion or miscarriages. The patient had lived in Brooklyn all her life. She had no bad habits. The family history was unimportant.

*Examination.*—This revealed a woman, lying in bed and appearing acutely ill; the face was flushed; the lips were parched; there was sordes of the teeth. The temperature was 103.8 F.; the pulse rate, 124; the respiratory rate, 22, and the blood pressure, 124 systolic and 88 diastolic. The lungs were clear, and the heart was normal except for an increased rate. The abdomen was distended moderately; there was no rigidity or peritoneal rebound. The spleen was palpable; there was some tenderness over the edge of the liver just below the right costal margin; no fluid wave was present in the abdomen. Pelvic examination revealed a nulliparous introitus; the cervix was small, hard and closed, in the axis of the vagina; the uterus was small, firm and anteverted; the adnexa were normal. The red blood cells numbered 2,660,000; the hemoglobin was 53 per cent; the white blood cells numbered 13,400. A differential count showed: polymorphonuclears, 85 per cent; lymphocytes, 4 per cent, and monocytes, 1 per cent. The urine contained a faint trace of albumin. Chemical analysis of the blood showed 15.9 mg. of urea nitrogen, 1.3 mg. of creatinine. Van den Bergh's test gave a positive delayed reaction, both direct and indirect. The icteric index was 111; the Wassermann reaction was negative. A blood smear was negative for malarial parasites. The Widal test gave negative results.

The patient continued to have chills and a temperature ranging from 98 to 105 F., with a pulse rate varying between 104 and 140. The respiratory rate ranged between 30 and 36.

On September 1, when the temperature was 103.6 F., the pulse rate 110 and the respiratory rate 40, the patient complained of sharp pain in the lower portion of the right side of the abdomen. Examination revealed a distended abdomen with rigidity over the entire right side, but more marked in an area about 2 inches (5 cm.) to the right of the umbilicus. The condition suggested a perforation of the ileum with peritonitis.

*Treatment and Course.*—A laparotomy was performed under spinal anesthesia. A large amount of free fluid was found in the abdomen. The liver was studded with many abscesses containing free pus. There was a pylephlebitis. The wall of the gallbladder was thickened, edematous and contracted. The spleen was enlarged to about three times its normal size. A culture of the pus was taken. A small abscess with surrounding hepatic tissue was excised. A gauze strip was placed down to the bed of the liver, and the abdomen was hurriedly closed because of the patient's poor condition. Dextrose and insulin intravenously and saline solution by clysis were given immediately, as was also intravenous stimulation. The patient died that evening at 9:15 p. m., after becoming comatose at 6 p. m.

A culture showed gram-negative bacilli and gram-positive diplococci.

*Autopsy.*—When the abdomen was opened, a diffuse, fresh, fibropurulent peritonitis was found. A large collection of exudate was found between the diaphragm and the dome of the right hepatic lobe. Several loops of the small intestine were fixed in the lower part of the abdomen in the cecal region. After separating the adhesions, a small pus pocket filled with creamy greenish-yellow pus was found surrounded by dark, almost black granulations. This pus pocket was adjacent to the cecum and revealed the stump of a spontaneously amputated appendix projecting into the cavity.

Examination of the portal vein revealed occlusion by firm reddish-gray thrombus masses at the place where the mesenteric vein empties. Following the



Fig. 2.—Low power magnification of a portal vein cut longitudinally. The vein is filled with thrombus masses. The periportal connective tissue shows edema, cellular infiltration and distended lymphatics.

portal vein toward the liver a gradual breaking down of the thrombus could be noted, and at the place where the main stem of the portal vein branched into the liver, greenish-yellow, creamy pus was found in place of the thrombus. Sections of the liver showed that the purulent thrombophlebitis spread far into the smaller branches. There were also connected with the lesions of the vein numerous abscesses of the liver of various sizes, the largest of which exceeded the size of a goose egg.

The spleen was enlarged to about three times its normal size. Its capsule was tense. Section showed a dark red pulp with well developed trabeculi.

*CASE 3.—History.*—M. F., a woman, aged 25, married, was admitted to the hospital on Sept. 23, 1931, complaining of pain in the epigastrium and the right

lower quadrant, nausea and vomiting. Two weeks prior to admission the patient had had an attack of pain in the epigastric region accompanied by nausea and vomiting which lasted four days. Then the symptoms subsided. She had had four similar attacks within the last two years. A week prior to admission, when she began to menstruate, the attack recurred and localized itself to the right lower quadrant.

*Examination.*—On admission, the temperature was 105 F.; the pulse rate, 112; the respiratory rate, 28, and the blood pressure, 120 systolic and 70 diastolic. Examination revealed an adult female patient lying in bed, appearing acutely ill; the face was flushed. There was a noticeable icteric tint to the sclera. There were a few fine crepitant râles in the right side of the chest posteriorly. The heart sounds were regular but rapid. No murmurs were heard, and the heart was not enlarged. The abdomen was tender in the right upper and right lower quadrants, and was somewhat distended. There was spasticity of the entire right rectus muscle, which was more marked over McBurney's point. There was no rebound tenderness. The spleen was easily palpable. A vaginal examination revealed a multiparous introitus; the cervix was in the normal axis and closed; the uterus was in the normal position. The left adnexa were normal, but the right fornix presented a sense of resistance and tenderness. The red blood cells numbered 4,530,000; the hemoglobin was 90 per cent; the white blood cells numbered 15,200. A differential count showed: polymorphonuclears, 89 per cent; lymphocytes, 9 per cent, monocytes, 1 per cent, and eosinophils, 1 per cent. Urinalysis was entirely negative. Pancreatic ferment tests gave negative results. The blood sugar was 116 mg. and the urine negative before a sugar tolerance test, which showed: blood sugar, 160 mg. and urine negative at the end of half an hour; blood sugar, 228.6 mg. and urine 9 per cent sugar at the end of one and one-half hours; blood sugar, 173.8 mg. and urine 3 per cent sugar at the end of two hours. The icteric index was 19. The reaction to the direct van den Bergh test was positive.

A diagnosis of a suppurative pylephlebitis following an appendical inflammation and accompanied by cholecystitis was made.

*Treatment and Course.*—On September 24, an exploratory laparotomy was performed under spinal anesthesia. There was a slight amount of free serous fluid. The gallbladder was normal except for edema and inflammation of the ampulla and the cystic duct. No calculi were found; the edge of the liver was round. The entire pancreas was normal. The spleen was slightly enlarged and beefy. The portal vein was markedly edematous, injected and thickened. The uterus and adnexa were normal. The major portion of the appendix was hidden by a mass of adhesions formed by contiguous cecum and omentum. The omentum was markedly injected and bled easily on separation, which brought to view an acutely inflamed appendix with small areas of necrosis on it and an abscess in the meso-appendix. No fat necrosis was present. The entire abdominal viscera were inspected. The appendix was removed by electrocautery after ligating and cutting the meso-appendix. The stump was inverted into the cecum by means of a purse-string suture. A gauze strip was inserted into the appendicular area through a stab wound to the right of the right rectus incision. The abdomen was closed in layers.

After operation, dextrose and insulin were given intravenously and saline solution by clysis. The abdominal wound drained profusely. On September 26 (the second day after operation), the patient suddenly became cyanotic and dyspneic and began to perspire profusely. The temperature dropped to 100 F., and the pulse rate to 110 a minute. The respiratory rate increased to 36 per minute.



Examination revealed a marked dilatation of the stomach, which was relieved by lavage. Examination of the chest was negative. The administration of dextrose intravenously was continued, the patient being unable to take anything by mouth because of nausea. On September 29, drainage from the abdominal wound was profuse; the temperature was 102.4 F.; the pulse rate, 130, and the respiratory rate, 32. The abdomen was distended, and the patient was nauseated. An enema produced fair results. A gastric lavage was given, with fair results. On September 30, a transfusion of 250 cc. of whole blood was given by the Koster method. A cannula was sewn into the vein in order to have a continuous intravenous infusion of 10 per cent dextrose in physiologic solution of sodium



Fig. 3.—Cross-section of a large intrahepatic branch of the portal vein. The vessel wall shows cellular infiltration and is hardly distinguishable from the surrounding periportal tissue. Remnants of hyaline thrombus material form a band lining the wall of the vessel. Inside a new lumen has formed by suppuration and is partly filled with masses of leukocytes.

chloride. The temperature was 102.4 F.; the pulse rate, 160, and the respiratory rate, 44. The patient's condition was becoming more critical. The abdomen was distended again, and the drainage was marked. The pulse rate continued to rise steadily in spite of various medications, such as digifolin. The temperature rose to 105.4 F. The patient died at 5:30 p. m. the same day.

*Postmortem Observations.*—As the abdomen was opened there was a gush of serohemorrhagic, purulent fluid. The small intestine and the stomach were markedly distended up to about 1½ feet (45.72 cm.) from the ileocecal junction,

where the remaining part was kinked up by adhesions, causing an obstruction. A slough was present around the lateral pelvic and the abdominal wall where the appendix had been removed. The spleen was about three times the normal size. The pancreas was normal. On cross-section, both the spleen and the pancreas appeared normal. There was no thrombosis of the splenic or the pancreatic veins. The liver seemed normal in size, but on cross-section there were many areas of abscess formation around the portal triads. The portal vein was thrombotic and suppurative for about 3 inches (7.6 cm.) from its entrance into the liver. The kidneys were normal.

**Microscopic Appearance:** The wall of the portal vein was surrounded by ample, well vascularized and edematous granulation tissue. The wall proper was also edematous; the fibrils were in loose arrangement, and most of the elastic tissue was broken up (as shown by special stains). Closely attached to the intima was a thrombus consisting mostly of fibrin which was canalized, the lumen being filled with pus. Examination of the liver proper showed many small and large abscesses which originated from the branches of the portal vein. In most places the portal vein was completely destroyed. The abscesses were walled off only by a layer of large phagocytes and outside of this by a narrow zone of granulation tissue. The relationship of these abscesses to the portal vein was brought out by the presence of bile ducts adjacent to the abscess or by remnants of a thrombus in the periphery of the abscess cavity. In many areas free from abscess there were infiltrations of the periportal fields with round cells and leukocytes and occasionally quite massive granulation tissue. These findings indicated a subacute character of the pylephlebitic lesion.

**CASE 4.—History.**—F. R., a woman, aged 47, was admitted to the hospital on June 25, 1929, complaining of chills, fever and sweats. Chills began four weeks prior to admission and were followed by high fever and sweats. This syndrome recurred daily. She had lost 20 pounds (9 Kg.) in the last three weeks.

The past history revealed that for three years the patient had had some vague abdominal distress referable to the right upper quadrant and the epigastrium. The patient had been treated for pyelitis about thirteen years previously. She was married twenty-six years prior to admission, and had four children who were living and well. Her habits were good. The family history was irrelevant.

**Examination.**—This revealed an undernourished adult, who appeared acutely ill. The temperature was 101.6 F.; the pulse rate, 120; the respiratory rate, 24, and the blood pressure, 120 systolic and 66 diastolic. Examination of the chest revealed equal expansion on both sides; the breath sounds were normal; there were no râles. The heart was not enlarged; the apex beat was normal but slightly rapid, and there were no murmurs. The abdomen presented tenderness in the right upper quadrant and the epigastrium. The edge of the liver was palpable about 2 fingerbreadths below the right costal margin. The kidneys were not palpable. No other points of tenderness or masses were palpable in the abdomen except for a slightly enlarged spleen.

Urinalysis showed a trace of albumin and a few white blood cells, but was negative for sugar. The hemoglobin was 62 per cent; the red blood cells numbered 3,370,000; the white blood cells, 8,000. A differential count showed: polymorphonuclears, 64 per cent; lymphocytes, 32 per cent; monocytes, 2 per cent, and eosinophils, 2 per cent. A blood culture and stool culture were taken, but both were reported negative after seventy-two hours. A blood smear taken for malarial parasites was negative. Chemical analysis of the blood showed: urea nitrogen, 14 mg.; creatinine, 1.5 mg.; uric acid, 2.72 mg.; dextrose, 117.6 mg., and carbon dioxide, 64 mg.

A diagnosis of abscess of the liver or pylephlebitis was made.

The patient was given dextrose intravenously and saline solution by clysis. Fluids were forced, and alcohol sponge baths were given for fever when necessary. On June 26, severe chills occurred which lasted thirty-five minutes, and the temperature rose to 106.2 F. after the chills. The pulse rate was 120; the respiratory rate, 24. A blood smear and blood culture were taken during the chills, both of which were reported as negative. The patient continued to have chills, fever and sweats until July 1, when a roentgenogram of the chest and the upper part of the abdomen showed a slight elevation of the right side of the diaphragm with limitation of motion and suggested abscess of the liver.

*Treatment and Course.*—On July 2, a laparotomy was performed under spinal anesthesia. The findings included many old adhesions of the gallbladder and omentum. The wall of the gallbladder was thickened and distended and contained a purulent fluid (empyema). There were thrombosis and varicosities of the cystic vein. On cutting into the cystic vein, free pus was demonstrated. The dome of the liver was free and not adherent to the diaphragm. Small multiple abscesses of the liver were found involving all the lobes. Free serous fluid was found in the abdominal cavity. The appendix was retroceally bound down by one old adhesion to the cecum, but was not inflamed. The spleen was enlarged to about twice its normal size. The wall of the portal vein was edematous.

The procedure was to cauterize all visible abscesses with the electrocautery. The gallbladder was removed after the cystic duct and vessels were ligated and cut. One gauze strip was placed in the bed of the gallbladder. Two other gauze strips were used to wall off the larger abscessed cavities. A specimen of the pus from the abscess of the liver was taken for examination and culture. The abdomen was closed in layers.

As soon as the patient was put to bed, dextrose intravenously with insulin and saline solution by clysis were given. Stimulation was given because of the poor quality of the pulse. Early the next morning the patient's condition was poor. Only one heart sound was heard at the apex, and pulmonary edema was setting in. The patient died at 11:30 a. m.

A smear of pus and a culture revealed gram-positive cocci.

*Postmortem Observations.*—The gastro-intestinal tract was apparently normal. The spleen was twice the normal size. The kidneys and pancreas were normal. There was no thrombosis of the splenic or the mesenteric veins. Examination of the liver showed absence of the gallbladder, with the cystic vessels and the cystic duct separately ligated with catgut. There was a purulent thrombophlebitis involving the cystic veins and extending by means of the portal vein into the liver and resulting in multiple abscesses of the liver at the portal triads. Some of the abscesses of the liver had been charred by means of the electrocautery. On cross-section, the liver showed multiple abscesses varying in size from that of a pinhead to that of a large pea.

Microscopic examination was similar to that in case 3. The pathologic report on the gallbladder was acute cholecystitis.

#### COMMENT

Pylephlebitis and abscess of the liver cannot be considered as synonymous; the latter is almost invariably the sequel to the former, but not all abscesses of the liver result from suppurative inflammation in the portal vein. The abscess may arise through four channels; the

portal veins, the hepatic artery, the bile ducts and possibly the lymphatics. It is only when the infection travels by way of the portal veins that there can be both pylephlebitis and hepatic abscesses, and even then the two need not be associated. If the abscess is single and the result of septic extension from the appendical veins, it is almost always found in the right lobe of the liver.

Serege<sup>1</sup> injected Chinese ink into the splenic veins of dogs and found particles only in the left lobe of the liver. When the injection was made into the large mesenteric vein, particles were found only in the right lobe. These findings were confirmed by Glenard;<sup>2</sup> however, Bauer<sup>3</sup> and others were unable to distinguish any difference in the distribution of the ink after injection into the splenic and the mesenteric veins, and they discredited the hypothesis of Serege and Glenard that a dual current existed in the portal veins. Bartlett, Corper and Long,<sup>4</sup> on examining microscopic sections of lobes of dog's liver after the injection of olive oil into the tributaries of the portal veins, came to the conclusion that there was a dual current and that blood from the stomach, spleen and duodenum and the first portion of the jejunum and rectum flowed mainly to the left lobe, while blood from the lower part of the jejunum, ileum and first portion of the large intestine flowed mainly to the right lobe. Dick<sup>5</sup> investigated the stream-line phenomena; he identified and studied the currents of the portal vein by placing a powerful electric light behind the vessel, thus satisfactorily transilluminating the moving blood currents. He was in this way able to demonstrate sharply segregated portal currents. The position of the currents varied with the tributary into which an injection was made; for example, when an injection was made into the splenic vein, the dye-stained blood was seen to enter the left side of the portal vein in a narrow stream, preserving a narrow ribbon-like course throughout the entire length of the portal vein. When dye was injected into one of the jejunal veins, a narrow abruptly demarcated stream was observed maintaining a constant undeviated course along the right wall of the portal vein. Following the dye into the liver he found, with few exceptions, that it was carried to fairly constant and definite areas in the liver from the various tributaries of the portal vein, which he used as the injection site. When the dye was injected into the splenic and gastric veins, it was conveyed to the left half of the liver almost entirely. Dye introduced into the veins of the upper part of the duodenum, the

1. Serege, H.: *J. de méd. de Bordeaux* **31**:271, 1901.

2. Glenard, F.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **3**:18 and 386, 1901.

3. Bauer, A.: *J. de l'anat. et physiol.* **45**:1, 1909.

4. Bartlett, F. K.; Corper, H. J., and Long, E. R.: *Am. J. Physiol.* **35**:36, 1914.

5. Dick, B. M.: *Edinburgh M. J.* **35**:533, 1928.

head of the pancreas and the jejunum was carried almost exclusively to the right lateral lobes of the liver. When injections were made into the colonic veins, the dye was distributed to all parts of the liver, but more particularly to the large lobe of the left side. In the instances in which the colonic veins did not form a common trunk, but had a separate combination in the large mesenteric veins, it was found that injection into the veins of the proximal colon produced a freer distribution of dye in the right half of the liver. These experiments are cited to offer a possible explanation for the greater frequency of right-sided solitary abscess of the liver. If the abscesses are multiple, they are distributed along the portal system, and the final picture is the resultant of forces tending toward segregation of abscesses on the one hand and toward confluence on the other.

In a review of the literature it is noticeable that there is a looseness in the use of the terms pylephlebitis and pyemic abscesses of the liver which is not only unwarranted, but also decidedly misleading. This is particularly true in quoting statistics of incidence and mortality. Thus it is possible to have pyemic abscesses resulting from invasion through the hepatic artery, in which instance no pylephlebitis is demonstrable. It can also be readily seen that there might be great differences in the results of treatment of abscesses of the liver following pylephlebitis and abscess of the liver due to dysentery.

Since Waller's<sup>6</sup> report of a case following appendicitis, there may have been many statistical contributions on the incidence of pylephlebitis. In 1886, Fitz<sup>7</sup> found the complication at autopsy in 11 of 257 cases of appendicitis. In 1897, Armstrong's<sup>8</sup> postmortem observations in 546 deaths for appendicitis showed pylephlebitis in more than 5 per cent. In 1903, Gerster<sup>9</sup> reported 1,189 operative cases of acute appendicitis in which pylephlebitis was a complication 9 times. This embraced his own experience from 1892 to 1901, at Mount Sinai Hospital, New York. In 1905, Munro<sup>10</sup> reported 15 undoubted cases. In the same year, Rendle Short<sup>11</sup> collected 1,000 cases of acute appendicitis with 4 instances of complicating pylephlebitis. In 1907, A. and E. Moschcowitz<sup>12</sup> reported 7 instances in 1,529 cases of appendicitis. In 1909, Giertz<sup>13</sup> published 4 cases occurring in 533 cases of appendicitis. In

6. Waller, quoted by Babler, E. A.: *Ann. Surg.* **61**:589, 1915.

7. Fitz, H. R.: *Am. J. M. Sc.* **92**:321, 1886.

8. Armstrong, G. E.: *Brit. M. J.* **2**:945, 1897.

9. Gerster, A. G.: *M. Rec.* **63**:1005, 1903.

10. Munro, J. C.: *Ann. Surg.* **42**:692, 1905.

11. Short, A. R.: *Index of Prognosis*, New York, William Wood & Company, 1918, p. 84.

12. Moschcowitz, A., and Moschcowitz, E.: *Arch. f. klin. Chir.* **3**:82, 1907.

13. Giertz, K. H.: *Ueber akute eitrig Wurmfortsatzperitonitis*, Munich, J. F. Bergmann, 1909.

1913, Braun<sup>14</sup> found it 8 times in 600 cases of appendicitis. Petré<sup>15</sup> found, during 1,340 autopsies after acute appendicitis, pylephlebitis in 5 per cent.

Colp,<sup>16</sup> reviewing all cases of appendicitis at Mount Sinai Hospital from 1916 to 1925, found that in 2,841 cases there were 9 instances of complicating pylephlebitis. In our 1,027 cases of acute appendicitis, we found pylephlebitis in 3 instances. Other statistical studies have been omitted because careful perusal and analysis reveal the indiscriminate grouping of the pylephlebitis with abscess of the liver of origin other than in infection of the portal vein.

Many cases of solitary abscess of the liver following appendicular inflammation have been reported. These are related to pylephlebitis only as the pathogenesis depends on a thrombophlebitis of the appendicular vein with the detachment of a septic embolus from a thrombus, its migration via the superior mesenteric and portal vein and lodgment in the liver with a resultant abscess. Or, as Quenu and Mathieu<sup>17</sup> insist, any aseptic embolus may travel the same route, reach the liver and produce a focus of necrosis, which is then capable of becoming infected by blood-borne organisms, but fundamentally the pathologic processes are different.

Thus, the important single cause of the condition is suppurative appendicitis. Langdon Brown<sup>18</sup> found acute appendicitis responsible for 42 per cent of 46 collected cases of pylephlebitis. However, infection in any organ the venous return from which empties into the portal vein may produce the complication.

One of the most characteristic signs of the disease is the change in temperature. Chills accompanied by a rapid rise in temperature, occurring in the progress of an acute inflammation of any organ in the abdominal cavity the veins from which drain into the portal system, must always be considered significant of entrance of septic material into the general circulation, after it passes through the liver. If it occurs before operation, it helps in arriving at a complete diagnosis, and if it occurs after operation it points toward a serious complication. The variations in temperature may occupy a wide range, from slight fluctuations between 101 or 102 F. to marked variations from 98 to 99 F. to 104, 105 or 106 F., as can be seen by comparing the fluctuations in case 2 with the changes in temperature in the other cases. The degree of variations or the degree of change in temperature daily is no indi-

14. Braun, H.: *Beitr. z. klin. Chir.* **86**:314, 1913.

15. Petré, G.: *Beitr. z. klin. Chir.* **94**:225, 1914.

16. Colp, R.: *Surg., Gynec. & Obst.* **43**:627, 1926.

17. Quenu, E., and Mathieu, P.: *Rev. de chir.* **44**:519, 1911.

18. Brown, L.: *St. Barth. Hosp. Rep.* **37**:95, 1901.

cation of the number of abscesses or the diffuseness of the lesion in the liver. Profuse perspiration is a frequent accompaniment of the daily chill. The chill need not necessarily be daily. Remission in both the chill and the rise in temperature may occur even though the disease has progressed to quite a considerable degree.

Pain over the liver is not an invariable accompaniment of the lesion, and its inconstancy helps make the diagnosis more difficult. When present, it is usually dull, is located in the right upper quadrant and has extension to the shoulder blades. A review of the case reports presented in the literature shows that but little emphasis is laid on pain as a symptom of pylephlebitis.

Whereas a high leukocytosis would be expected with an infection of this kind, it does not always occur. In the 4 cases herein reported the white cell count ranged from 8,000 to 15,000. It is particularly significant that the case in which the blood count was 8,000 was one in which the pylephlebitis complicated an empyema of the gallbladder. In the differential count, the polymorphonuclears ranged from 60 to 89 per cent. Thus, the leukocyte count also cannot be considered of great diagnostic significance.

Tenderness is almost invariably present, although it may be so slight as to be considered negligible. It may frequently be found directly over the portal vein.

Jaundice is almost always present and is one of the early signs of involvement of the liver. When it appears early in the disease (before the diagnosis of appendicitis, cholecystitis, etc., is made), it may be misleading, as it may draw attention away from a causative appendicitis and direct it to the biliary passages in a case in which involvement of the latter is only the terminal complication. This occurred in case 3. In many of the reported instances the bilirubin content of the blood serum showed a progressive increase long before the jaundice could be noted clinically. The appearance of jaundice as a postoperative complication of appendicitis should arouse suspicion of the development of a complicating pylephlebitis. A slight icteric tint to the sclerae may appear even before the chill and fever.

In the description of the pathologic processes found at autopsy in cases of pylephlebitis, enlargement of the spleen is mentioned in a great many of the cases reported. In this connection it seems strange that little mention is made of splenic enlargement as a clinical sign of value in pointing toward the diagnosis. In all of our cases enlargement was noticed clinically, and it seems to us that it may be utilized as a valuable diagnostic sign. The presence of serous fluid in the peritoneal cavity in small amounts is expected because of the general peritoneal reaction to the inflammation even of an organ in direct continuity to it. With

complete obstruction of the portal vein, however, the development of ascites is far more likely to occur. This, however, is not seen except terminally. Of the other symptoms of anorexia, nausea, vomiting, lassitude and emaciation, little need be said, because they are not characteristic of this condition any more than they are of infectious conditions any place in the body. Examination of the blood for organisms is of little value in these cases, because in most instances the invading organism is *Bacillus coli*, which rarely breaks into the blood and if it does is quickly destroyed there.

In the typical case the diagnosis can be made by the shift of symptoms from the appendicular region to the hepatic region following repeated chills and fever, in addition to the other symptoms and signs enumerated, all occurring in the absence of manifestations of extensive peritonitis. Munro's<sup>10</sup> dictum that the "most important clue in making a diagnosis is the recognition of the causative appendicitis," while true in most instances, is certainly not universally applicable, as case 4 shows. It must therefore be remembered that the original focus may be in any organ in the abdomen, venous drainage from which empties into the portal system.

The treatment of this condition is primarily prophylactic, and such prophylaxis may be accomplished in two ways. There can be no doubt that if all cases of acute appendicitis were to come to operation at an earlier date through earlier recognition of the condition, there would be fewer cases of pylephlebitis. When, however, the surgeon encounters a case of appendicitis and notes in cutting the meso-appendix that there is no bleeding because of thrombosis of the appendical vein, he should consider that case as one in which pylephlebitis may develop. This is true whether there is a history of chills or not. Remembering, however, the low incidence of occurrence of this grave complication and also that thrombosis of the appendical veins is encountered quite frequently in gangrenous appendicitis and perhaps less frequently in the acute suppurative type of inflammation, the question of whether it is possible to determine in which of these cases pylephlebitis will develop presents itself. Since many acutely inflamed appendixes contain definitely thrombosed veins, and since the patients in whom they are found make uneventful recoveries after simple appendectomy, apparently because the early appendectomy removed the primary bacterial focus and also because even if bacteria are sent to the liver from the thrombosed veins they are apparently destroyed by that organ the bactericidal properties of which are potent, it becomes apparent that in the absence of more data it is impossible to predetermine in which cases complications will develop.



If at operation a frank suppurative phlebitis of the mesentery is evident, before resorting to and before performing the appendectomy a ligation or excision of the ileocolic vein is indicated. The method of procedure that may be adopted is any one of the following: Gerster<sup>9</sup> advocated incision and evacuation of the infected thrombosed vein. This is best done by opening the veins in the stump of the appendix and following them up on the cecum and into the ileocecal angle as far as there is suppuration, evacuating the thrombosed vessels and instituting drainage by means of gauze. Wilms<sup>19</sup> advocated ligation of the veins in the ileocolic angle for reasons similar to those advocated by Trendelenburg in ligating the ovarian veins in cases of puerperal pyemia. This is done by immobilizing the cecum and ascending colon from the posterior abdominal wall, exposing the veins, which are then tied without occluding the artery. Drainage is placed to the cecum. The variation in the venous return from the ileocecal angle makes it difficult to ligate all the venous channels successfully, and it must be remembered that unless all the veins at the angle are ligated the purpose of the operation may easily be defeated. Another objection to the procedure is the danger of destroying the circulation with resultant gangrene of the bowel. Braun<sup>14</sup> described ligation of the ileocolic vein, since this vein is the only channel through which the thrombi in the appendical vein can travel to reach the portal vein. Its ligation is a rational procedure in the attempt to arrest the bed of infection. When the infection has already spread beyond the confines of the ileocolic vein and a pylephlebitis has already developed, operative intervention is of no value unless a well defined abscess has developed, in which case the indication, of course, is for incision and drainage. The literature on the value of ligation of the portal vein in cases of pylephlebitis is clearly reviewed by Colp,<sup>16</sup> and the conclusion is that such an operation is probably never indicated, even though the experimental studies of Neuhof<sup>20</sup> and operative attempts on human beings (Beer<sup>21</sup>) have demonstrated that the "hepatopetal" veins in the gastrohepatic omentum in certain persons can efficiently carry on the portal circulation after complete occlusion of the portal vein by ligation. For if the vein is not yet the seat of thrombosis and suppuration, because of the small percentage of incidence of pylephlebitis, there is great likelihood of its remaining free. If it is believed that it may become infected by extension, then ligation or, preferably, resection of the ileocolic vein, a relatively simple procedure, is likely to prevent the extension. When infection of the portal vein and the intrahepatic portion of the portal

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19. Wilms, M.: *Zentralbl. f. Chir.* **36**:1041, 1909.

20. Neuhof, H.: *Surg., Gynec. & Obst.* **16**:481, 1913.

21. Beer, E.: *Am. J. M. Sc.* **150**:548, 1915.

system has already occurred, all that can be expected of ligation of the portal vein is the demonstration of the ability of the anastomotic veins of the gastrohepatic omentum to relieve engorgement of the abdominal viscera drained by the portal system on the one hand and an interruption of the bacterial feeding process from the original focus of infection on the other. Neither of these, however, influences the outcome, because there are already enough infection and damage of the liver, and also a remaining focus for more dissemination in that portion of the thrombosed and infected vein central to the ligature. Indeed, many cases have been reported in which complete thrombosis of the portal vein existed at the time of operation, and in such instances, even on theoretical grounds, ligation can scarcely be of value.

It must also be remembered that when the process has extended because ligation or resection of the ileocolic vein has not been successful in preventing the spread from the primary thrombus, the patient may occasionally recover.

# ELECTROBASOGRAPHIC METHOD OF RECORDING GAIT

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Conditions due to neuromuscular and vascular pathologic processes together with deformities of the lower extremities are generally recognized causes of disturbances in locomotion. The treatment of these disorders embraces the fields of medicine, general surgery and orthopedics. Whenever treatment of such conditions is seriously undertaken, the difficulties accompanying the visual analysis of gait are recognized.

Efforts directed toward the development of methods for recording gait have been less numerous than the apparent need for such clinical advantage would seem to justify. Most of the studies in this country and abroad have been made with a consideration for the physiology of locomotion without reference to the possibility of such studies being of practical value to the various branches of clinical medicine.

We accept the premise that no two people walk alike. We doubt the possibility of determining a normal gait. Our position is comparable to that of Wunderlich's and others in establishing clinical thermometry. All of us accept the fact that of a hundred people who show no evidence of disease, records of their respective temperatures would not be identical. Nevertheless, 98.6 F. has become the point from which elevated and subnormal temperatures are measured. Moreover, the temperature chart is used as an index of the progress of treatment. Our efforts have likewise been directed toward the development of a method of recording gait for the purpose of providing a series of clinical records by which the progress of treatment may be expressed through the precision of physical laws. The diagnosis in terms of localization and etiology of abnormal gait must continue to depend on the facts revealed by the individual history, physical examination and laboratory data.

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Read before the Robert Jones Orthopaedic Society, Rochester, N. Y., Nov. 5, 1932.

From the Department of Surgery, Division of Orthopaedics, Rochester University School of Medicine and Dentistry. Funds for this research work have been provided by the Rockefeller Foundation.

All methods heretofore developed for recording gait, including those that have been published by others and ourselves, have failed to be of practical clinical value. We consider the available evidence for this statement as foreign to the subject of this paper. One of us (R. P. S.) has stated the limitations of the basograph<sup>1</sup> as an instrument for recording gait, and the pneumographic method<sup>2</sup> must now be regarded in the light of prevailing fundamental difficulties which cannot be removed to provide the simplicity required for clinical application.

In addition to providing records with ease, rapidity and economy, any method of recording gait must fulfil the following requirements: 1. The mechanism must be free from the possibility of errors which would cause changes in the character of the record produced. 2. The character of the gait record of the same patient must be constant unless the gait is altered. 3. Changes in the gait record must be indicative of changes in the patient's gait.

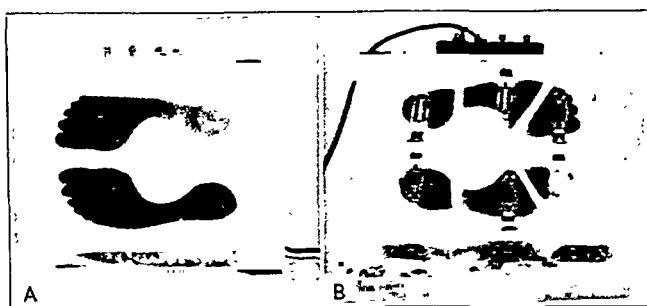


Fig. 1.—*A*, the transillumination box, front view, showing outline of feet on ground glass. *B*, the transillumination box, back view, showing lights in the three respective compartments for each foot.

A transillumination box (fig. 1) was developed in connection with the pneumographic method of recording gait. Through its use it was possible to determine the length of time that weight was borne on the heel, the head of the fifth metatarsal and the great toe of the respective feet. During locomotion weight is successively transmitted from the heel to the head of the fifth metatarsal, then to the great toe, which is last to leave the ground. When the patient walks without a limp, an equal amount of time will be spent on these respective points of the two feet. Abnormalities in gait are, therefore, the result of inequalities in time spent on the respective points of each foot, including the omission of weight-bearing on one or two of the three points on one or both feet.

1. Schwartz, R. P., and Vaeth, W. E.: A Method for Making Graphic Records of Normal and Pathologic Gaits, *J. A. M. A.* **90**:86 (Jan. 14) 1928.

2. Schwartz, R. P., and Heath, A. L.: The Pneumographic Method of Recording Gait, *J. Bone & Joint Surg.* **14**:783 (Oct.) 1932.

It is true that inequalities in pressure might be given consideration. At the present time we are in possession of evidence to support the belief that differences in the duration of time on these respective points can prevail with little or no inequality in pressure. We are of the opinion that whenever respective pressures are unequal there is an accompanying difference in the duration of weight-bearing time at that point on the respective feet. Evidence supports the belief that differences in the duration of time spent on these respective points can prevail with little or no inequality in pressure. Because of this it seems logical that a method of recording gait would be most reliable when it revealed differences in the duration of time that weight is borne on the heel, the fifth metatarsal and the great toe of the right and the left foot, respectively. The electrobasographic method of recording gait fulfils this requirement; it does not record pressure.

#### TECHNIC

The mechanism employed is as follows: Boards 42 feet (2,480.16 cm.) long and 17 inches (42.55 cm.) wide are covered with an aluminum plate. This forms the negative side of an electric circuit. On the soles of the patients' shoes (fig. 2) three-fourths inch (1.87 cm.) circular brass contacts are fastened by means of heated flake shellac. These contacts are placed under the heel, the fifth metatarsal and the great toe. The position has been determined on a mathematical basis, taking into consideration the total area of the particular shoes. For women's and children's shoes one-half inch (1.27 cm.) circular contacts are used. From these three contacts on the shoes three wires lead to a recording apparatus and the transillumination box (fig. 3).

The recording mechanism (fig. 3) consists of a one-tenth horse power direct current motor, a 48 to 1 gear reducer and a camera box in which a 100 foot roll of 70 mm. emulsion paper is driven past a horizontal slit. On the outside of the box, arranged opposite the slit, are seven 6 watt bulbs encircled by brass tubing 1 inch (2.5 cm.) in diameter. From each of these tubes another tube one-eighth inch (0.3 cm. in diameter, centered opposite the lamp filament, leads to the slit. The center light is connected to a metronome and is made to go on and off every second. This gives the timing line in terms of seconds in the middle of the paper, thereby dividing it into right and left halves. The light on the right end is connected to the contact on the right heel, the next one to the fifth metatarsal, and the third light on the right side is connected with the contact under the right great toe. The connections of the respective lights on the left side of the midline from without inward are the same: heel, fifth metatarsal and great toe. When the patient stands on the aluminum plate the lights will go on and off as these respective points of the shoes come in contact with the aluminum plate so as to close the circuit. The motor drives the paper through the camera box at a constant speed of  $10\frac{1}{2}$  feet (320 cm.) per minute. We are, therefore, able to record on the photographic paper, lines which represent the duration of time spent by the patient on the heel, fifth metatarsal and great toe of each foot. Moreover, we are able to determine the number of steps taken per minute.

The photographic record is developed in a dark room, as is the record produced by the electrocardiograph.

## RESULTS

A typical record of the gait of an apparently normal man, aged 30, is illustrated in figure 4*A*. The wide, broken line in the middle represents intervals of time in seconds. The lines representing the duration



Fig. 2.—Circular contacts applied to the right shoe for man, woman and child. These contacts form the positive side of an electric circuit.



Fig. 3.—Subject standing on aluminum-covered board; the wires are attached to contacts on the shoes; illumination of the right and left foot, respectively.

of weight-bearing on the heel, the fifth metatarsal and the first toe of the right and the left foot are shown on the respective sides from the edge toward the timing line.

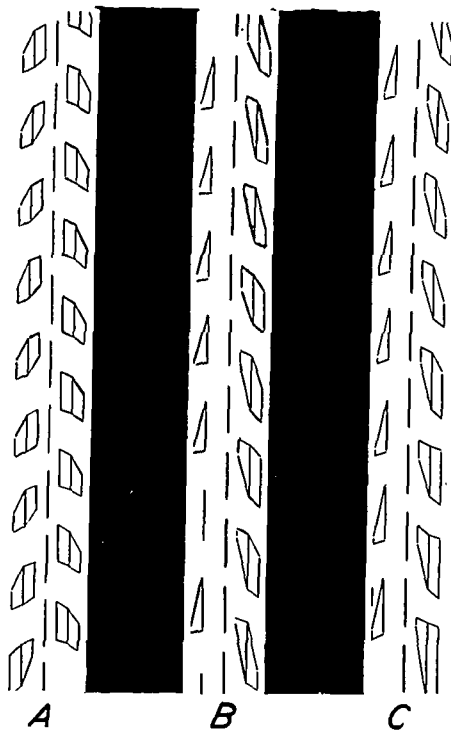


Fig. 4.—*A*, typical record of a “normal” man, H. T., aged 30, weighing 98 Kg. and 182 cm. in height. The lines representing the duration of weight-bearing on the heel, fifth metatarsal and first toe of the right and left foot, respectively, are indicated. The broad interrupted middle line indicates the time in seconds. *B*, gait record of J. S., aged 64, weighing 69.2 Kg. and 181.6 cm. in height. Lateral displacement of left scaphoid and cuboid. Note: (1) short duration of weight-bearing on left heel; (2) long duration of weight-bearing on left fifth metatarsal; (3) absence of weight-bearing on left first toe. *C*, record made on Sept. 29, 1932. Note duplication of the same patient’s record made on Sept. 28, 1932 (*B*).



Fig. 5.—Lateral and postero-anterior roentgenograms, showing medial displacement of forefoot at the level of the scaphoid and cuboid bones.

Having thus produced a "normal" record of the foregoing character, figure 4 *B* illustrates the abnormal gait of a man who had, on May 26, 1932, suffered a medial dislocation of the scaphoid and cuboid bones of the left foot. The roentgenograms of the affected foot are illustrated in figure 5. The prevailing deformity forced the left foot in a varus position accompanied by slight equinus. Again referring to figure 4 *B*, the timing line is the same length as in figure 4 *A*; the records are otherwise very different. The unaffected right foot bore weight for a period of 1.05 seconds, and the weight was thrust in normal sequence from the heel, which bore weight for 0.783 second, to the fifth metatarsal, which bore weight for 0.729 second; and the first toe, which is normally last to leave the ground, bore weight for 0.297 second. The left foot received weight for a period of 0.786 second, 0.088 second of which was spent on the heel, while the fifth metatarsal received weight for 0.735 second with no weight being transmitted to the left great toe.

*Weight-Bearing Time in Seconds*

	Total	Heel	Fifth Metatarsal	First Toe
Right foot.....	1.050	0.783	0.729	0.297
Left foot.....	0.786	0.088	0.735	0.000

This record was made on Sept. 28, 1932; the contacts were removed from the shoes, and the patient was returned to the division. On the next day, the patient was sent to the gait clinic; the contacts were again fastened to the shoes according to the mathematical determinations previously made, and a second record was made (fig. 4 *C*). This is presented as an example of the evidence which, at present, indicates that we may accept the following premise: So long as the patient's condition remains unchanged, successive records of gait will reveal the same characteristics. Any method for recording gait, to provide an index of the progress of treatment, as applied by the various branches of clinical medicine and surgery, must be free from differences in records due to causes other than changes in the patient's gait.

Further evidence that the electrobasographic method of recording gait has met this fundamental requirement is presented in figure 6. On Oct. 18, 1932, a small oxygen tank fell on the patient's right second toe, producing uncomplicated trauma of the whole toe. The first record of the patient's gait was made on the day injury was incurred. Successive records were made on October 20, 24, 27 and November 3. The last record reveals complete functional recovery at a time when the subjective symptoms and physical signs of trauma had disappeared.



This series of records further indicates that the electrobasographic method does record evidence of improvement in gait when treatment favors the passing of subjective symptoms and the disappearance of physical signs of the cause of dysfunction.

Between Sept. 9, 1932, and Nov. 28, 1932, one hundred and three records were made. Seventy records were of subjects showing no visual evidence of abnormal gait, while the remaining thirty-three were of those who revealed definite departure from "normal" locomotion. A series of twelve records of gait of "normal" persons is illustrated in figure 7.

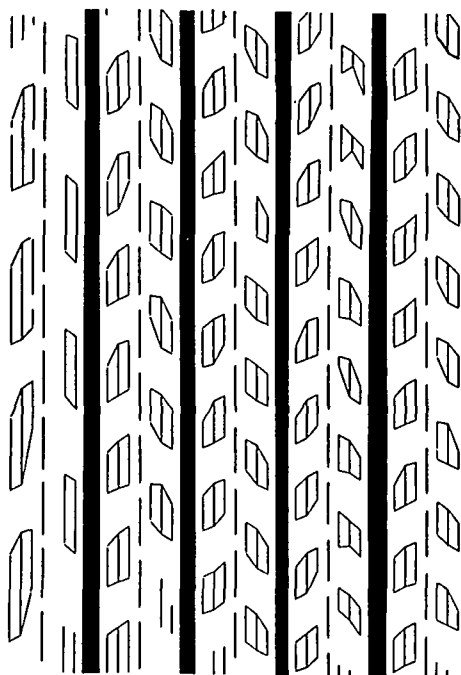


Fig. 6.—Gait records of Miss M. D., aged 33, weighing 48.5 Kg. and 161 cm. in height. Injury of right second toe with complete functional recovery as revealed by the gait records made between Oct. 18 and Nov. 3, 1932.

The detailed discussion of the interpretation of these records must receive consideration in the next paper on this subject. These twelve unselected records reveal a definite tendency toward uniformity in contour. This is particularly emphasized when comparison is made with the twelve records of gait of persons who had definite limitation in locomotion, as illustrated in figure 8. It is also evident that comparison of these records of abnormal gait, unselected for this purpose, reveals no tendency toward duplication, nor do they closely resemble the records in figure 7.

These two groups of records reveal the fact that "normal" gait may be recognized from the relationship of the lines representing the

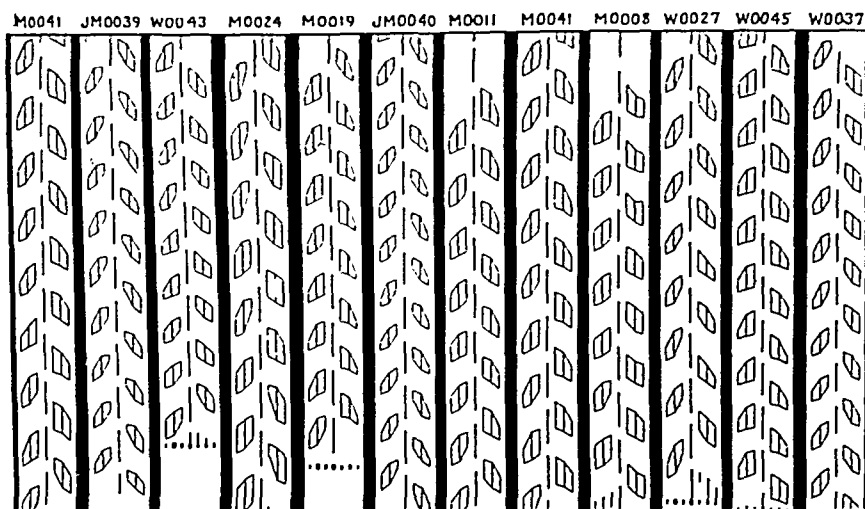


Fig. 7.—A series of twelve gait records of "normal" persons.

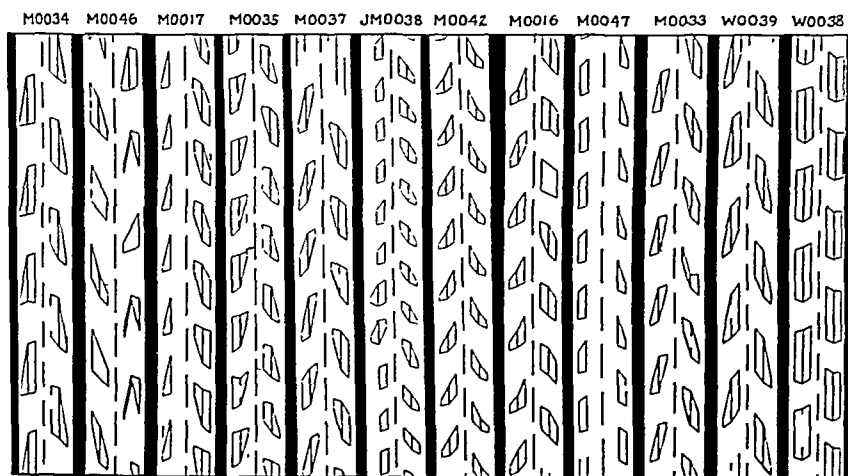


Fig. 8.—A series of twelve gait records of subjects who had definite limitations in locomotion: *M0034*, proliferative arthritis, both knees; *M0046*, degenerative arthritis; toe drop; *M0017*, medial displacement of forefoot at level of scaphoid and cuboid bones; *M0035*, right gluteus medius; *M0037*, epilepsy; *JM0038*, left equinus; *M0042*, athetosis; *M0016*, ankylosis, right hip in flexion; *M0047*, equinovarus with cavus; *M0033*, postoperative subastragalar arthrodesis for equinovarus following poliomyelitis; *W0039*, muscular dystrophy; *W0038*, muscular dystrophy.

duration of time that weight is borne on the heel, the fifth metatarsal and the great toe. Moreover, it has been demonstrated that the absence of equality in length or the omission of one or more of these lines may be accepted as evidence of "abnormal" locomotion.

#### SUMMARY

1. Medicine, general surgery, neurosurgery, industrial surgery and orthopedics have to do with the treatment of patients suffering from lesions which produce disturbances in gait.

2. A method of recording gait is as essential to the proper treatment of abnormal gait as is the electrocardiograph in the treatment of heart disease, or the thermometer in the recording of temperature.

3. Such clinical advantages may be provided by that method of recording gait which will meet the following conditions:

(A) It must assure simplicity of procedure, minimum time requirement and economy.

(B) The mechanism must be free from alterations in the record due to technical errors.

(C) Evidence must prove that changes in successive records made of the same patient's gait are due only to the way the patient walked on successive dates. Such records would then give evidence of the presence or absence of improvement under recorded conditions.

4. We have offered the premise that abnormalities in gait may be defined in terms of the duration of weight-bearing time on the heel, the fifth metatarsal and the great toe of the respective feet.

5. The electrobasographic method of recording gait photographs the duration of time that weight is borne on the heel, the fifth metatarsal and the great toe of each foot, using the patient's own shoes.

6. Data in the form of patient's records of gait have been presented to support the belief that the electrobasographic method of recording gait fulfils the provisions essential for providing the clinical advantages as outlined in 3 of the summary.

Dr. Milton Chapman, Dr. Edwin Fritz, Mr. Carson Meyer and Mr. Howard R. Patterson of the Eastman Kodak Company and Mr. F. W. James of the Bausch and Lomb Optical Company cooperated with us and assisted in this work. The continued interest of Dr. John J. Morton and Dr. Wallace Fenn has made possible the presentation of this work.

# HEALING OF FRACTURES AND BONE DEFECTS AFTER VENOUS STASIS

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AND

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In this paper we shall report a series of observations on the healing of fractures or of defects in both ulnae of the dog when the veins draining one foreleg are ligated, thus creating marked venous stasis in that leg.

## REVIEW OF THE LITERATURE

The literature on the effect of venous stasis on osteogenesis has been reviewed by Pearse and Morton,<sup>1</sup> who trace the use of hyperemia from the time of Ambroise Paré. The clinical observations in the literature stimulated these authors to study the subject experimentally. They created a small defect in the fibula of each hind leg and ligated the right popliteal vein in twelve dogs. The ligation of this vein caused venous stasis in the region of the experimental bone defect in that fibula. In eleven of the twelve dogs, union was accelerated on the side of the ligation; this was manifested by the earlier formation of callus, the earlier calcification of callus and the earlier union. In addition to the experimental work, Pearse and Morton reported two clinical cases of delayed union in which venous stasis (hyperemia) instituted by elastic compression resulted in union.

In a previous paper, Morton and Stabbins<sup>2</sup> reported observations made on twelve rats and three dogs in which 0.5 cm. of each fibula was removed and the left saphenous vein was ligated. In these animals nonunion occurred on the ligated side. The authors concluded that a partial block of the veins of a limb in which there is a fracture or a resection causes delay in the union. After this paper was published, one of us (Dr. Key) repeated the experiments of Morton and Stabbins on the fibulae of dogs, but the results were inconclusive and were not published. After the publication of the second paper, in which an opposite result was reported following a similar operative procedure, we felt that the observations should be confirmed. If it is true that venous

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From the Department of Surgery, Washington University School of Medicine.

1. Pearse, H. E., and Morton, J. J.: The Stimulation of Bone Growth by Venous Stasis, *J. Bone & Joint Surg.* **12**:97, 1930.

2. Morton, J. J., and Stabbins, S. J.: Circulatory Factors Influencing Normal Osteogenesis, *Ann. Surg.* **86**:430, 1927.

stasis stimulates osteogenesis and accelerates the union of bone, venous stasis constitutes, so far as we know, the only method yet discovered by which this can be accomplished.

Consequently, we resected 0.4 cm. of each fibula and ligated the popliteal vein in six dogs. Ten weeks later the animals were killed, and the fibulae were removed and studied. In one animal there was slightly firmer union on the right or ligated side, and in five animals the amount of callus and degree of union were practically the same on the control and on the ligated side.

From the aforementioned observations it is evident that we were not able to confirm the results either of Morton and Stabbins<sup>2</sup> or of Pearse and Morton.<sup>1</sup> We thought that the conflicting results might be explained by an unhappy choice of site for the bone defect. Since the fibula is a small bone and is largely covered by muscle attachments, it is difficult to perform a series of uniform subperiosteal resections on it. Consequently, we decided to repeat the experiment on a larger bone, and we chose the ulna because other experimental work had shown us that this is a bone of considerable size, and that since it is splinted by the radius, any desired amount can be resected with relatively little disability to the animal.

#### MATERIAL AND METHODS

The material consisted of twenty-four adult dogs. Twelve of the dogs were subjected to bilateral subperiosteal osteotomy of the ulna, the bone being exposed under aseptic conditions and cut with an osteotome and the wound sutured. In six of these dogs the ligation of the veins draining the right foreleg was carried out at the time of the operation on the ulna, and in the other six the unilateral venous ligation was carried out one week later.

The other twelve dogs were subjected to operations in which a piece of bone approximately 0.5 cm. in length was resected from the shaft of each ulna. The operation was the same as the preceding one, except that instead of the osteotome the sharp bone-cutting forceps were used. After the shaft of the ulna had been exposed subperiosteally approximately 0.5 cm. of the shaft was removed with the bone-cutting forceps, care being taken to remove the entire thickness of the shaft and to make the defects in the ulnae of a given animal as nearly the same size as possible. In six of these animals the unilateral venous ligation was carried out simultaneously with the resection of the ulna, and in the remaining six the ligation of the veins was performed one week after the osteotomy.

In ligating the veins an incision was made first over the lower third of the brachial artery, and the deep veins accompanying this artery were tied and cut. Likewise, any other veins which could be found in this vicinity were tied and cut. This ligation caused congestion in the foreleg. Then a rather long incision was made in the bend of the elbow, and the large superficial veins which cross the elbow joint were ligated. Finally, a small incision was made in the vicinity of the olecranon, and a superficial vein which was usually present in this region was ligated. We thus performed ligation of all of the large veins which could be identified in the region of the elbow. In each instance the vein was doubly ligated and cut between the ligatures.

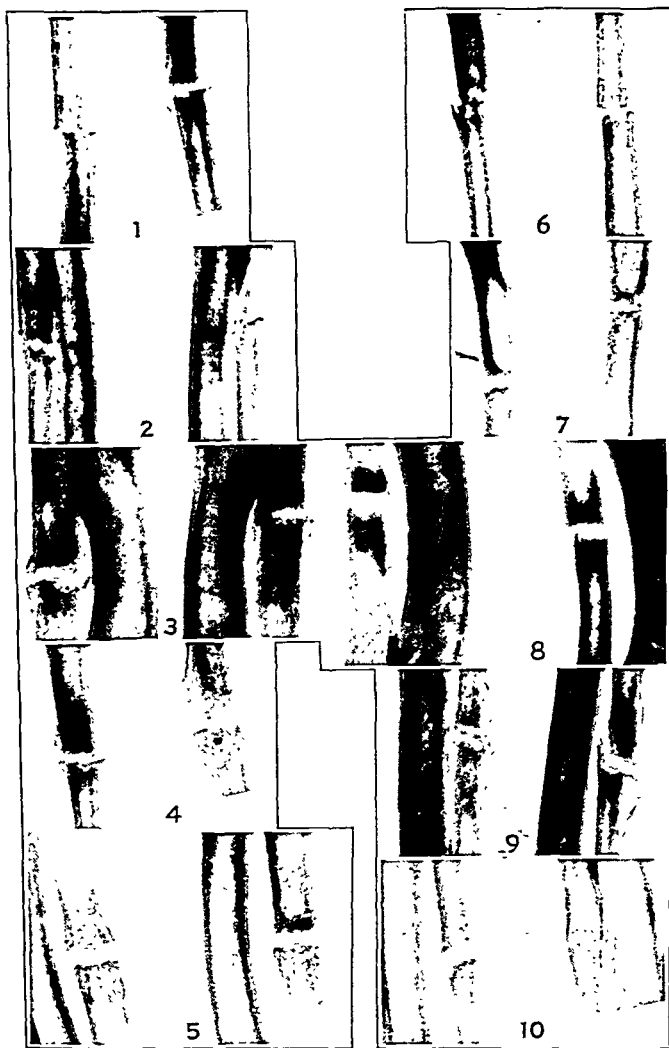


Fig. 1 (parts 1 to 10, inclusive.—Roentgenograms of the ulnae of dogs after osteotomy. In each instance the veins draining the right foreleg were ligated at the elbow. In parts 1 to 5, inclusive, the ligations were performed at the time of the osteotomy, and in parts 6 to 10, inclusive, the ligations were performed seven days after the osteotomy. In each instance the x-ray photograph of the ulna of the ligated limb is on the left and the control is on the right. Pictures 1 and 6 show the condition after four weeks; 2 and 7, after five weeks; 3 and 8 after six weeks; 4 and 9 after eight weeks; 5 and 10 after ten weeks.

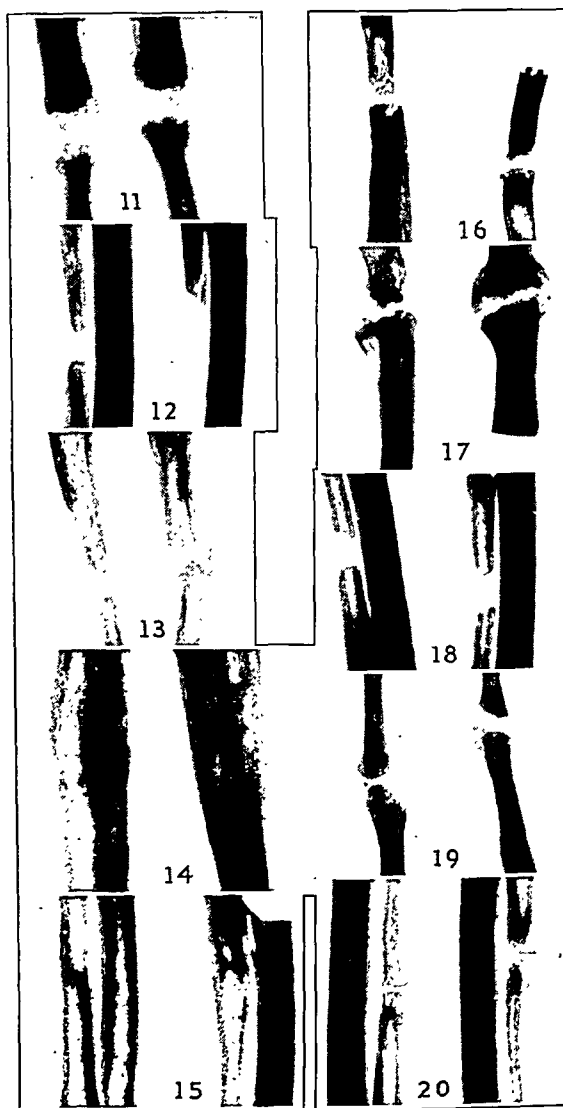


Fig. 2 (parts 11 to 20, inclusive).—Roentgenograms of operative defects in the ulnae of dogs in which the veins draining the right foreleg had been ligated at the level of the elbow. In parts 11 to 15, inclusive, the ligations were performed at the time the defects were made, while in parts 16 to 20, inclusive, the ligations were performed one week later. In each instance the ulna of the ligated leg is on the left and the control is on the right. Roentgenograms 11 and 16 were taken after four weeks; 12 and 17, after five weeks; 13 and 18, after seven weeks; 14 and 19, after nine weeks; 15 and 20, after twelve weeks.

The operation on the veins always resulted in marked venous congestion of the foreleg and foot. The swelling persisted over a period of about two weeks and then decreased gradually as the circulation became adjusted. Our object in delaying the ligation of the veins until one week after the osteotomy in half of our animals was to rule out the possibility of accelerated union resulting from the presence of an unusually large hematoma at the site of the fracture or bone defect.

The animals in which osteotomies had been performed were killed at intervals of from three to ten weeks, and those with bone defects, at intervals of from three to twelve weeks. The ulnae on both sides were removed and examined and fixed in a diluted solution of formaldehyde (1:10). U. S. P. Roentgenograms of the specimens were made, and the specimens were then decalcified, sectioned, stained and studied microscopically.

#### RESULTS

The gross specimens disclosed no demonstrable difference in degree of union between the ulna of the leg which had been subjected to ligation of the veins and the control on the other side of the animal. Nor was any difference shown in the roentgenograms (fig. 1, 1 to 10) or on microscopic examination. In some instances union was more advanced than in other experiments of the same or of longer duration, but this was due to the fact that the dogs were young ones; in these (fig. 2, 14 and 15) there was approximately the same degree of union on both the ligated and the control side. There was no more bone atrophy on the ligated than on the control side.

On microscopic examination engorged, apparently dilated blood vessels were seen in the region of the fracture or defect on the ligated side, but study of the sections from the fracture or defect on the control side of the same animal revealed a similar condition.

#### COMMENT

In a recent paper Pearse and Morton<sup>3</sup> reconsidered their first opinion that blocking of the venous circulation tends to cause non-union. They pointed out that their first operations were not carefully performed, and that the ligation of the saphenous vein was probably not effective in creating venous stasis in the region of the fracture. They further noted that ligation of the small saphenous veins has no effect on the rate of union in the fibula, while resection of the femoral artery and its branches tends to cause delayed union.

It is difficult to correlate the results of Pearse and Morton<sup>3</sup> with those obtained in the experiments reported in this paper. There are possible sources of error in each method. In our work it is possible that, in spite of the extensive ligation and severance of all of the veins

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3. Pearse, H. E., and Morton, J. J.: The Influence of Alterations in the Circulation on the Repair of Bone. *J. Bone & Joint Surg.* 13:68, 1931.



sufficiently large to be identified in the region of the elbow, the venous stasis was neither of sufficient degree nor of sufficiently long duration to influence the repair of the ulnar fractures. On the other hand, there was no question but that a marked degree of venous stasis was obtained; this lasted over a period of about two weeks, and then the limb gradually returned to a condition resembling that on the control side. The possible error in the experiments of Pearse and Morton is in the fact that the fibula is a small bone the surface of which is largely covered by muscle attachments. In our experience, conclusions drawn from experimental fractures or resections on this bone have not been reliable.

In regard to the clinical cases reported in the literature and those of Pearse and Morton in which fractures (with delayed union) united after passive hyperemia was instituted, we may state that we have had similar experiences. After reading Pearse and Morton's paper we used the method clinically and obtained union. But we are not in a position to state that the union was due to the hyperemia.

#### CONCLUSIONS

Ligation of the veins around the elbow caused venous congestion in the foreleg and foot of the dog, but had no effect on the healing of a fracture or of a defect in the ulna of this leg.

# RIBS OVERLYING EMPYEMA CAVITIES

## PATHOLOGIC STUDY

J. DEWEY BISGARD, M.D.

OMAHA

Transformation of the external form of ribs overlying empyema cavities occurs so constantly that the nature of the transformation and its pathogenesis seemed worthy of investigation. An extensive search of the literature failed to provide information dealing with the subject, with the exception of descriptions of the gross deformities of ribs (Hedblom<sup>1</sup>).

These ribs, as every surgeon engaged in thoracic surgery has frequently observed, have lost their normal contour and have become relatively round, triangular or rectangular and somewhat larger in cross-sectional dimensions. As illustrated in figure 2 *A*, these changes have resulted from the deposition of subperiosteal new bone on the inferior borders and internal surfaces of the ribs. The greatest deposits are laid down along the angles of the ribs and taper off with the pleural reflections at both extremities, where they become quite normal in appearance. Since adjacent ribs frequently are in contact or overlap, synostoses occasionally occur. Likewise, there occur certain concomitant or subsequent alterations of the internal architecture of these deformed ribs.

However, only those ribs and only those portions of the ribs which shelter, or present evidence of having sheltered, empyema cavities show these changes. Evidence of the original extent of empyema cavities has been obtained from roentgenograms taken during the acute stage of the disease and before the establishment of drainage, or from the extent of the thickened pleura as observed in the course of extensive plastic operations or at necropsy.

Some of the material from which these observations were made and brief histories of the cases from which some of the specimens were obtained follow.

## REPORT OF CASES

CASE 1.—H. E. M., a boy, 15 months of age, was admitted on May 7, 1932, to the University Hospital with a history of cough, fever and increasing respiratory difficulty for three weeks. From the classic physical and roentgenographic findings

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From the Department of Surgery, University of Michigan.

1. Hedblom, C. A.: Deformity of the Thorax Secondary to Pleural or Pulmonary Disease, J. A. M. A. **94**:162 (Jan. 18) 1930.

and the presence of thick pus containing pneumococci, type I, aspirated from the left pleural cavity, a diagnosis of postpneumonic empyema was made.

Daily thoracenteses were carried out for one week. Open drainage was then established and the empyema cavity rapidly became obliterated, so that after three weeks there remained only a short residual sinus. However, two months after admission, death resulted from purulent pericarditis following an intercurrent infection of the upper respiratory tract.

At autopsy an investigation of all the ribs of the left half of the thorax was made. New bone had been deposited on the inferior edges and internal surfaces of all ribs with the exception of the upper two and lower three, in which no alteration could be made out on gross examination. The greatest deposits occurred at the angles, while at the extreme ends of the ribs no abnormality was dis-

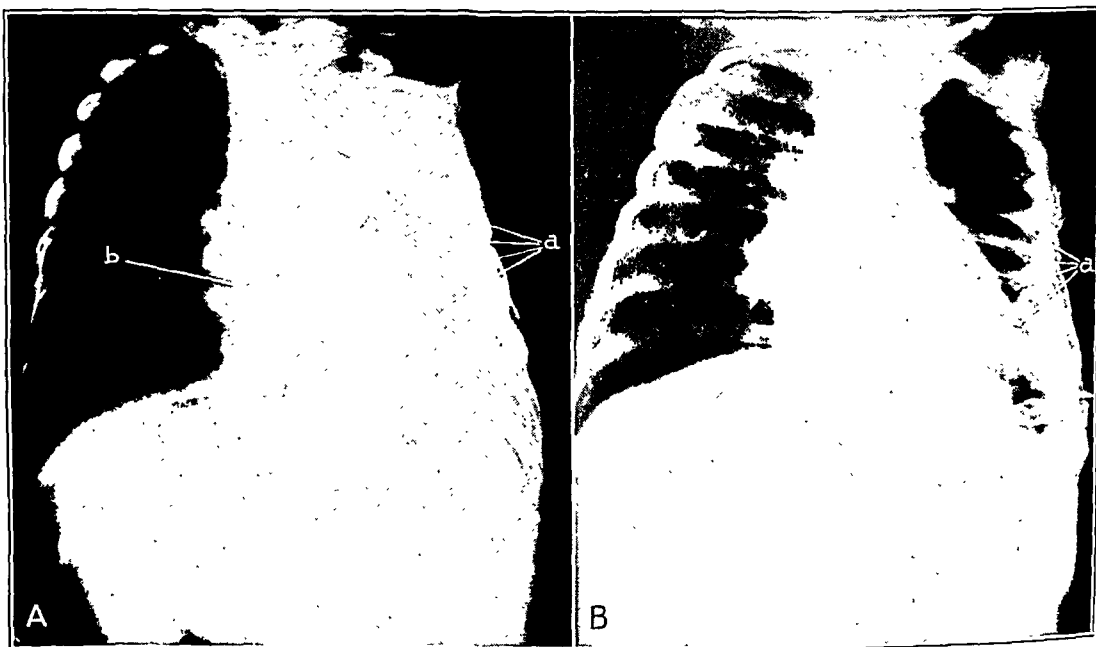


Fig. 1 (case 1).—An undrained acute empyema of less than three weeks' duration: *a*, shadows cast by new-formed bone along the inferior surfaces of ribs 4 to 9 inclusive; *b*, the apex of the functional scoliosis resulting from protective reflex muscle spasm. The narrowing of intercostal spaces frequently observed in chronic empyema is absent. *B*, roentgenogram of the same patient eleven days later and four days after the establishment of drainage. The shadows of new-formed bone (*a*) stand out distinctly against the contrast medium provided by the pneumothorax.

cernible. This is well illustrated in figure 2 *B*, a roentgenogram of the anterior half of one of the ribs. Corresponding to the distribution of new bone deposits, the underlying parietal pleura was firm, dense and thick.

Roentgenograms taken on the patient's admission to the hospital (fig. 1 *A*, before drainage) and a week later (fig. 1 *B*, after drainage) clearly show a layer of new bone along the inferior edge of each rib overlying the empyema cavity. It is important to note that these changes occurred within three weeks after the onset of illness.

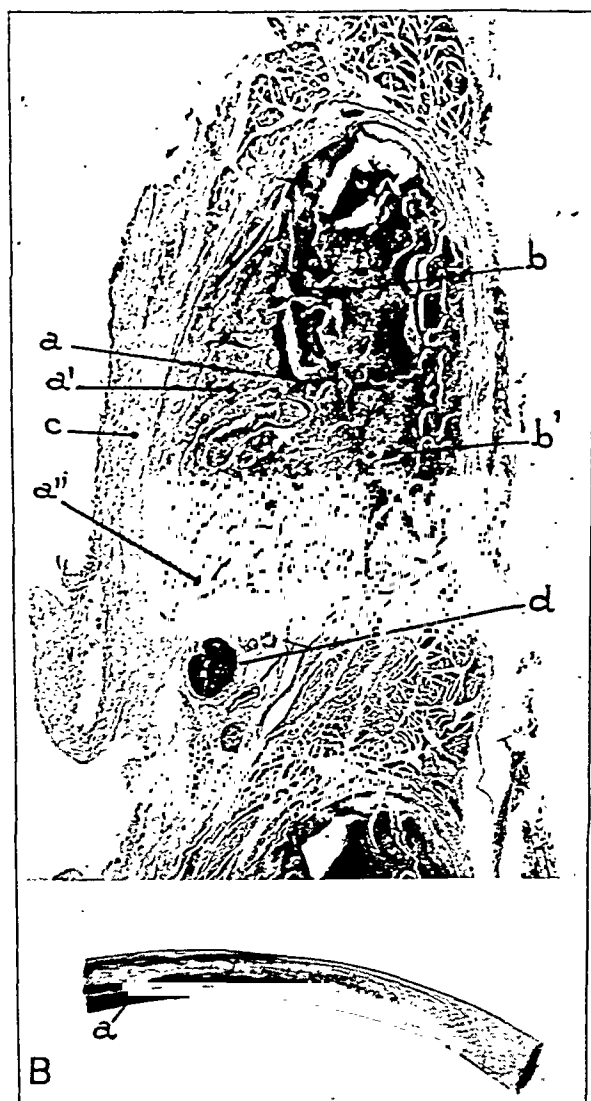


Fig. 2 (case 1).—*A*, upper cross-section of a triangularly shaped rib which overlaid the empyema cavity shown in figure 1. The three strata of new-formed bone (both spongy and dense) responsible for the alteration of the shape of the rib are designated by *a*, *a'*, *a''*; the original internal surface which is buried by new bone and undergoing absorption at *b'* is designated by *b*, the inflamed and greatly thickened parietal pleura and periosteum by *c*, and the intercostal nerve and blood vessels by *d*. Note that the new bone has been deposited on the surfaces adjacent to the inflamed parietal pleura and intercostal blood vessels and that the rib was originally oval in contour. *B*, roentgenogram of the anterior half of the rib illustrated in cross-section in *A*. The newly deposited bone (*a*) diminishes in amount progressively toward the sternal extremity, where for a short distance there is no new bone. On the external surface the cortical thickening from peripheral condensation of trabeculae is apparent.

Two adjoining ribs with their intercostal tissues, periosteum and parietal pleura were cross-sectioned *en masse*. A photomicrograph of the specimen (fig. 2 *A*) demonstrates the intimate relation of the new-formed bone to the thickened parietal pleura and the intercostal vessels and its limitation to the surfaces in contact with these structures. It is apparent that this new-formed bone has been deposited in three distinct layers on the old cortex which, although still

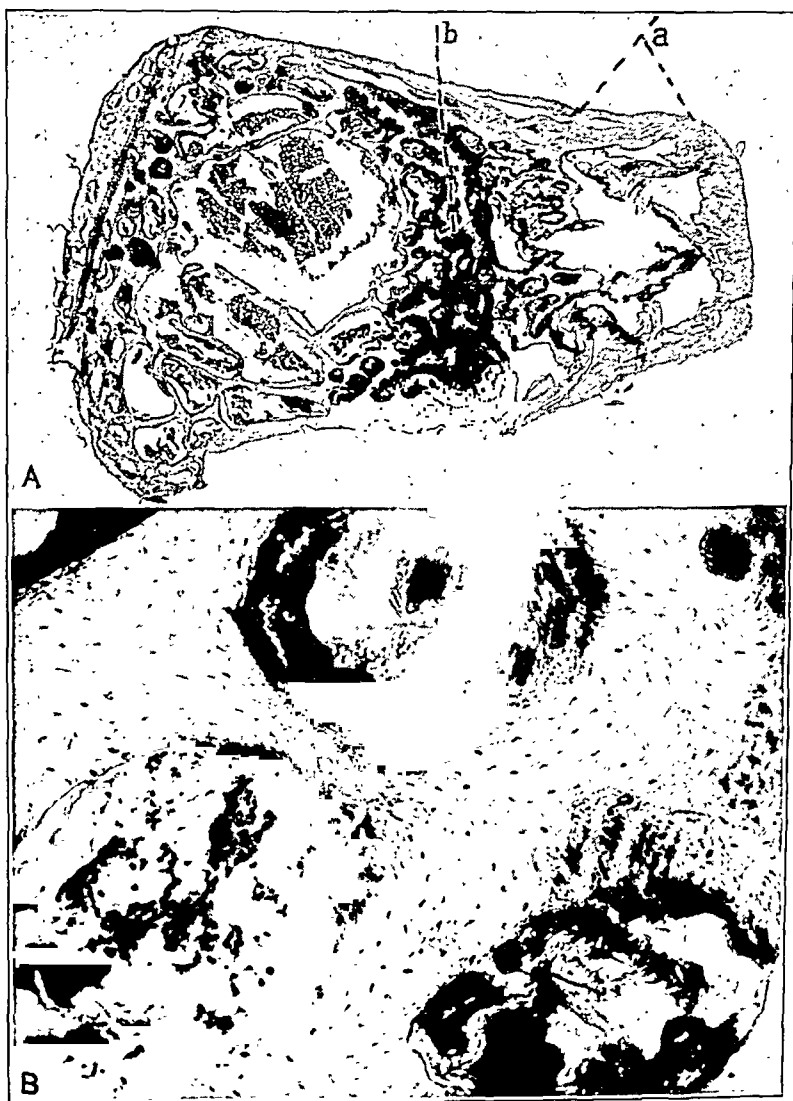


Fig. 3 (case 2).—*A*, photomicrograph of one of the rectangular transformed ribs removed at operation. The old cortex (*b*) which originally was in contact with the inflamed parietal pleura but which is now buried by newly deposited bone (*a*) is surrounded by calcified fibrous marrow. *B*, high power photomicrograph of the calcified fibrous bone marrow illustrated in *A*.

intact, is undergoing absorption, especially at the inferior angle. As a consequence of this transformation the rib has lost its normal oval contour and has become larger and triangular-shaped. The significance of these observations will be considered in the comment.

CASE 2.—C. B., a boy of 15 years was admitted to the University Hospital on July 8, 1929, for treatment of a postpneumonic empyema of the right pleural cavity. The onset of pneumonia had occurred seven weeks previously. Drainage was established immediately on admission, and four months later a Schede thoracoplasty was done to obliterate a large residual cavity with its broncho-pleural fistula.

Figure 3*A*, a low power photomicrograph of a cross-section of one of the ribs, depicts the extensive alteration of external conformation. The new bone, as noted in the preceding case, has been deposited on the cortical surface adjacent to the pleura and in this instance has given the rib a relatively rectangular shape.

Of great interest is the presence of calcified fibrous marrow localized principally about that portion of the old cortex which is enclosed within the newly deposited bone. These changes are represented in greater detail in figure 3*B* and their possible significance will be considered in the comment.

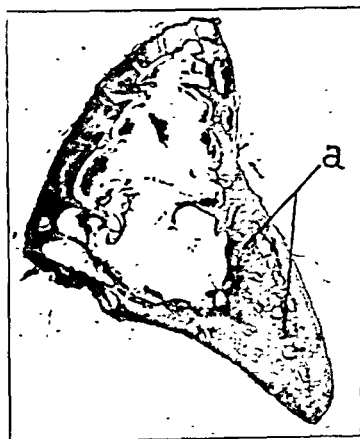


Fig. 4 (case 3).—From the deposition of new bone (*a*) on the inferior mesial aspect, the contour of the rib, normally oval, has become triangular. Throughout, the bone is extremely dense, probably the result of chronicity of the empyema in a child. The portion of the original cortex buried by the abnormal bone deposit has been absorbed.

The roentgenogram, figure 9*B*, clearly reveals that the greatest new bone deposits have occurred at the angle, and that the old bone contains an increased number of trabeculae, with definite condensation of these trabeculae about the periphery, especially along the external cortical surface.

CASE 3.—N. S., a boy, aged 5 years, was admitted to the University Hospital on March 5, 1929, with a postpneumonic empyema of the left pleural cavity, which subsequently was proved by biopsy to be tuberculous. A discharging sinus had been present continuously since the establishment of drainage soon after the onset of the disease, two years and three months before admission.

To obliterate a large empyema cavity and to close an associated bronchial fistula, a Schede thoracoplasty was done in stages in January, 1930.

One of the ribs removed at operation (approximately three years after the onset of the empyema) was sectioned for microscopic study. As illustrated in figure 4, extensive transformation of the rib has occurred. In cross-section it is considerably enlarged and definitely triangular. The cortex is abnormally thick

and composed of abnormally dense bone. As has occurred in all cases which have been studied, the new bone has been deposited on the surface of the rib adjacent to the pleura and the intercostal blood vessels. The portion of the original cortex on which the new bone was laid down has been entirely absorbed.

CASE 4.—A. W., a white man, aged 22 years, entered the University Hospital on Dec. 8, 1929, for the treatment of a chronic, postpneumonic nontuberculous empyema of ten months' duration. Soon after the onset of empyema, intercostal drainage had been established, but one month later the sinus had been permitted to close. Subsequently spontaneous drainage through a bronchus had occurred.

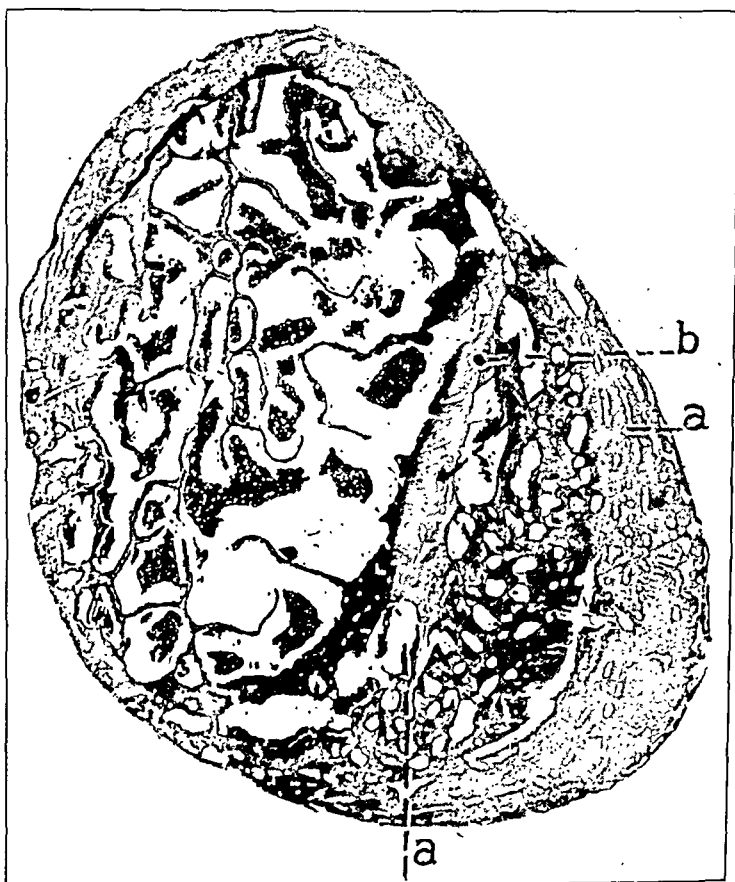


Fig. 5 (case 4).—The outline of the original cortex of the transformed rib is definitely oval. The new bone (*a*) has been laid down in several layers under that portion of the periosteum which is in contact with the intercostal blood vessels and inflamed parietal pleura. The new bone is rather dense and the marrow adjacent to the buried old cortex (*b*) presented in several sections fibrous tissue replacement of the normal marrow tissue.

On the day following admission, adequate dependent open drainage was established and prompt obliteration of the cavity ensued.

The alterations of external conformation and of the internal architecture of the rib resected approximately five months after the onset of the empyema are depicted in figures 5 and 9 C. The new bone has been laid down on the inner

surface and inferior border of the rib in semicompact concentric lamellae. The portion of the old cortex on which the new bone has been deposited has remained intact. In some marrow spaces of the old bone there has been replacement of normal marrow by fibrous tissue.

The roentgenogram of this rib (fig. 9C) brings out the dense newly deposited bone in sharp contrast to the less dense old bone. The other evidences of transformation noted in the previously described specimens are present but to a lesser degree.

#### EXPERIMENTAL OBSERVATIONS

EXPERIMENT 1.—Dog 78F, an adult mongrel police dog, weighing 14 Kg., was operated on. After a subperiosteal resection of a 3.5 cm. segment of the right

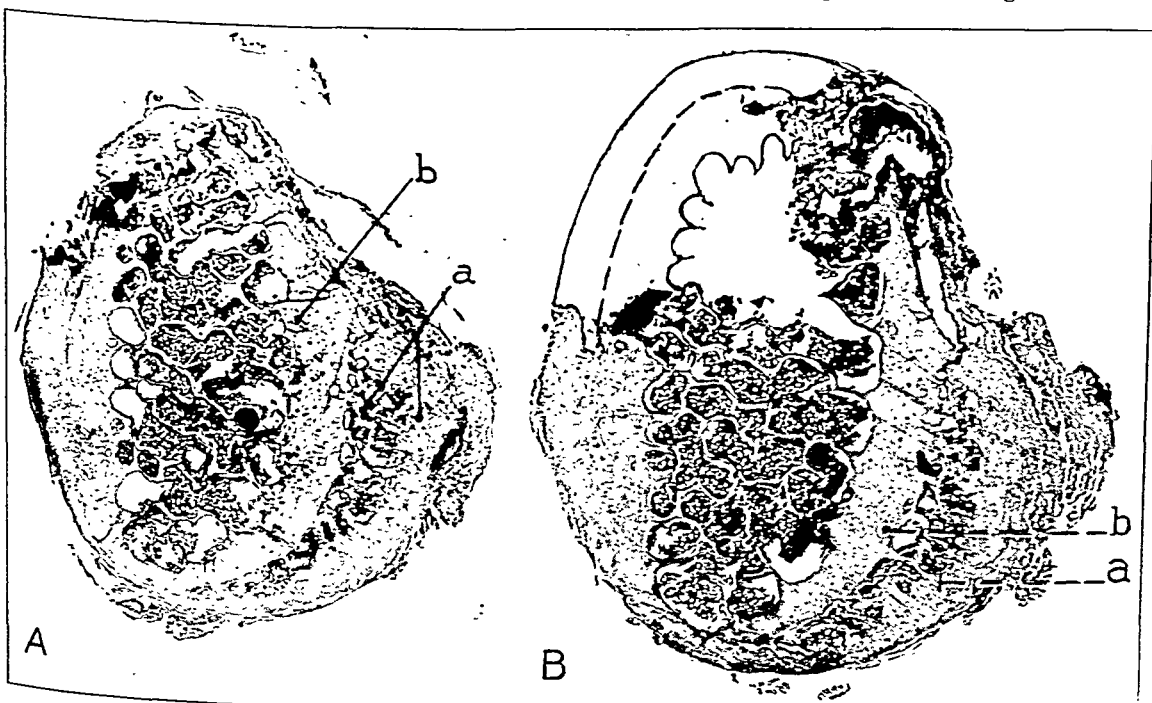


Fig. 6.—Ribs from experimental animal in experiments 1 (A) and 2 (B). Typical subperiosteal new bone (a) has been laid down on the cortex (b) under that portion of the periosteum which normally is in contact with the parietal pleura. The gross architecture of the old rib has been reproduced. Compare these specimens with the human specimen in figure 2A.

tenth rib at its angle, the endothoracic cleavage plane was established and an extra-pleural pneumolysis was performed; the parietal pleura was gently freed from the periosteum of ribs 9, 8 and 7 and their respective intercostal structures for a distance of approximately 10 cm. Into the space created by the pneumolysis, gauze was gently packed and the wound closed without drainage.

Healing occurred by primary intention, but on the third postoperative day and on four subsequent occasions it was necessary to aspirate considerable serosanguineous fluid from the subcutaneous and deeper tissues.

Six weeks after operation the animal was killed and at autopsy there was a small subcutaneous collection of serous fluid containing flecks of fibrin and com-



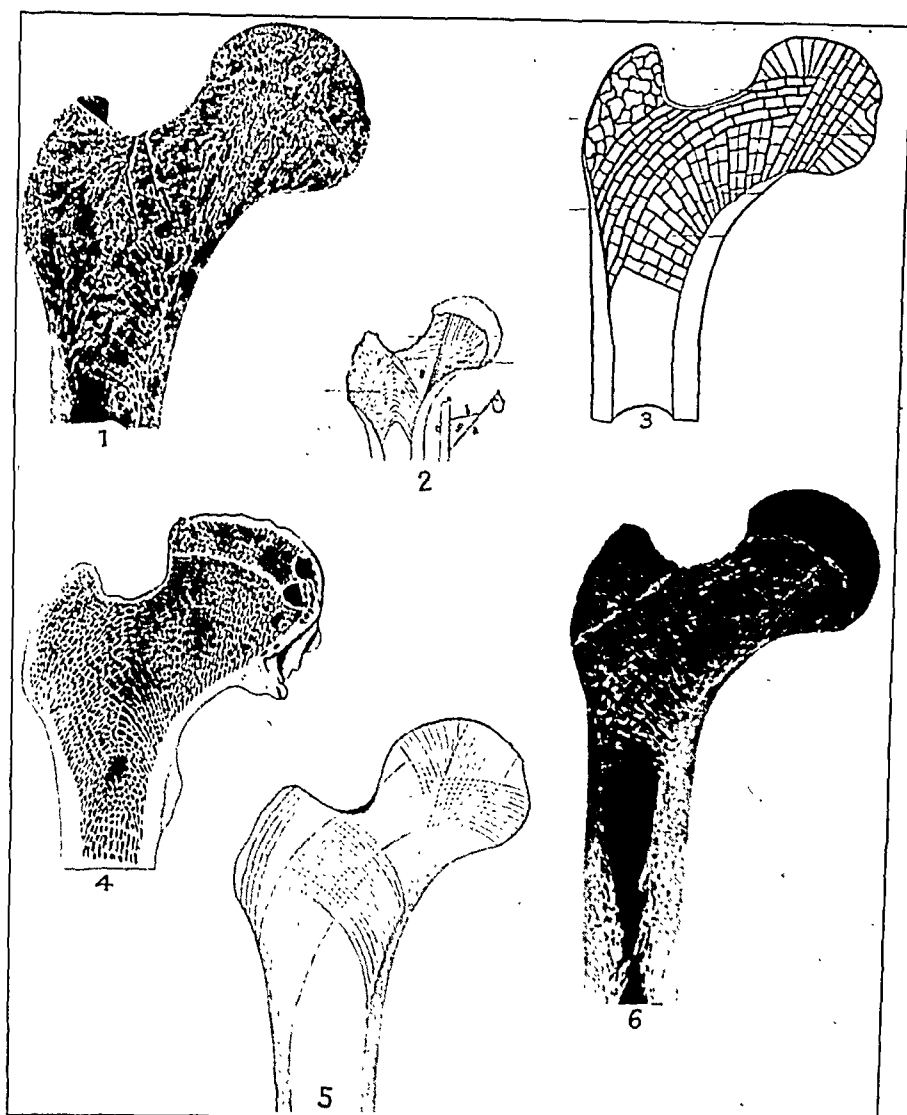


Fig. 7.—Reproduction of an illustration from Wolff (*Das Gesetz der Transformation der Knochen*, Berlin, A. Hirschwald, 1892): Nos. 1 and 6, photographs of the bony architecture of the proximal portion of the shaft and of the head and neck of the normal femur. No. 2, this crude but effective analogy of the mechanical support given by trabeculae to the overhanging head and neck on the shaft of the femur for the transmission of the forces of weight-bearing to the mechanics of the lamp-post bracket was first used by Ward, an English anatomist. Nos. 3 and 4, diagrammatic representations of the inner or trabecular architecture, demonstrating the two principal systems of trabeculae; the compression system arising from the adductor side of the cortex of the shaft and extending in a fan-shaped arrangement to the greater trochanter and the opposite surfaces of the head and neck, and the traction or tensile system which arises from the cortex of the abductor side of the shaft and extends in a wide arch to the adductor portion of the head. These systems are supplemented by smaller groups; they always course either perpendicularly or parallel to the axis of the bone, and intersect at right angles. No. 5, diagrammatic illustration of the courses of the trabecular systems described.

municating with the subcostal space. The gauze pack was rather firmly fixed to the greatly thickened pleura and to the chest wall by a fibrinous exudate and some granulation tissue. The inner, or that portion of the periosteum in contact with the gauze was greatly thickened, edematous and vascular. It separated from the ribs with abnormal ease. The normal oval contour of each rib had been altered by a layer of new bone on its internal surface, the extent corresponding exactly to that of the inflamed portion of the periosteum with which it was in contact.

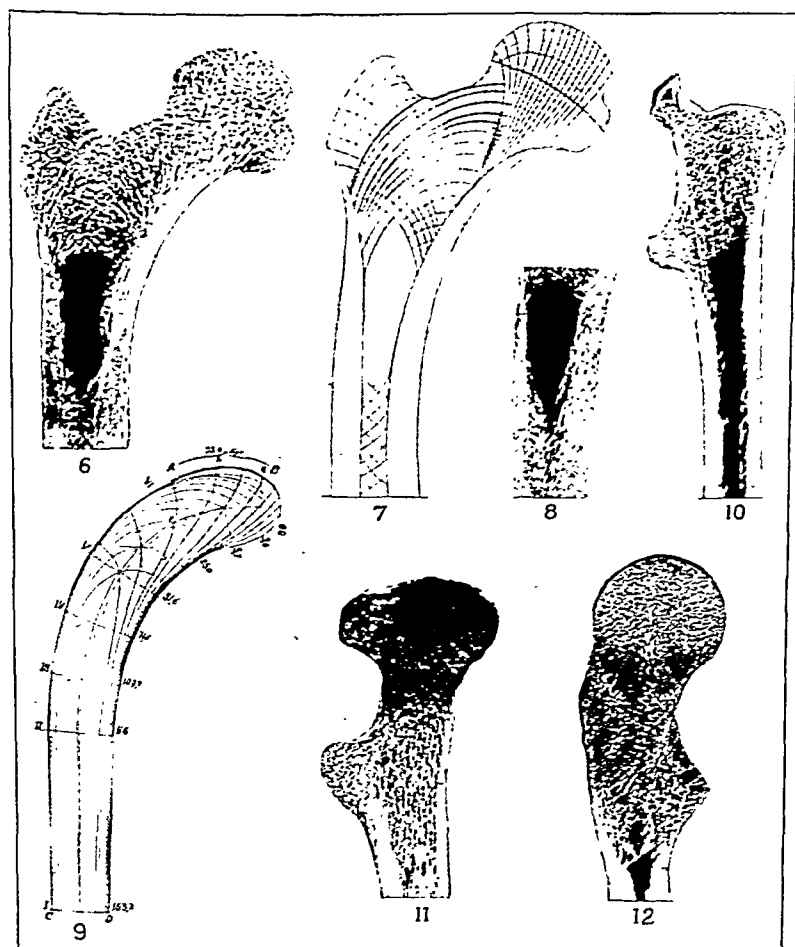


Fig. 8.—Reproduction of an illustration taken from Wolff (*Das Gesetz der Transformation der Knochen*): Nos. 6, 8, 10, 11 and 12. Sections of the femoral head, neck and shaft which were cut in various planes for a complete analysis and reconstruction of the trabecular systems. The mathematical basis of Wolff's law is depicted in the striking similarity of the diagrammatic representation of the trabecular systems (7) to the graphic representation of the distribution of forces in their various components (mathematically calculated) in a structure, the Fairbairn crane (9), which is similar in shape and function to the human femur.

As revealed by microscopic examination (fig. 6 A) of a cross-section of one of these ribs (the eighth), the transformation had resulted from the deposition of

a crescent of subperiosteal new bone on the old cortex, histologically not unlike that observed in the human specimens (figs. 2*A* and 5), a newly formed subperiosteal cortex of dense bone with a central spongiosa of trabeculae and of fatty and cellular marrow.

EXPERIMENT 2.—Dog 84F, an adult shepherd dog, weighing 12.5 Kg., was operated on. With a technic similar to that of the pectoral muscle pneumolysis described by Alexander,<sup>2</sup> long segments of ribs 7, 8, 9 and 10 were stripped of their periosteal sheaths, and a muscle flap raised from the chest wall and fashioned with a pedicle to preserve an adequate blood supply was insinuated between the internal surfaces of the bare ribs and the mesially displaced periosteum and intercostal bundles. The wound was closed in layers and healed by primary

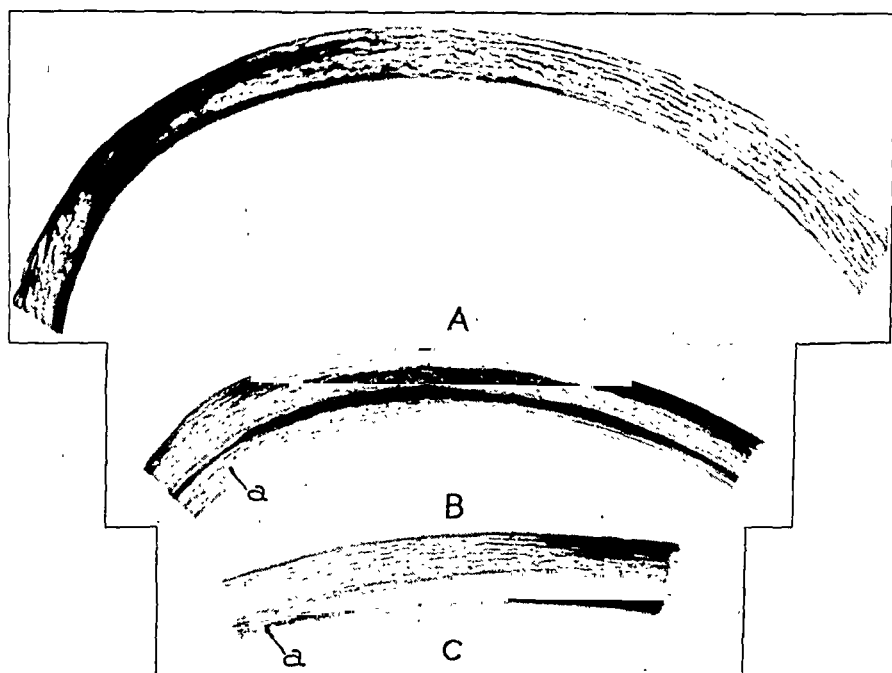


Fig. 9.—*A*, roentgenogram of a normal rib with the flat surface against the film. Posterior to its angle the rib becomes relatively round and its cortex thicker, and its spongiosa contains fewer trabeculae, which cross diagonally from one opposing cortical surface to the other. In the anterior portion the longitudinal trabeculae can be demonstrated traversing the long axis of the rib for long distances, and the cortex is very thin. *B*, roentgenogram of a transformed rib removed in case 2. Note the new-formed bone (*a*) deposited in greatest quantities at the angle of the rib and in progressively smaller quantities anteriorly. In comparison with the normal rib structure in *A*, the cortex is greatly thickened at the expense of the trabeculae of the spongiosa. *C*, roentgenogram of a rib removed in case 4. There is an increase of trabeculae, no thickening of the cortex, but the newly deposited bone (*a*) on the inner surface is very dense. The greatest density and quantity are found at the angle.

2. Alexander, John: Supraperiosteal and Subcostal Pneumonolysis with Filling of Pectoral Muscles, *Arch. Surg.*, to be published.

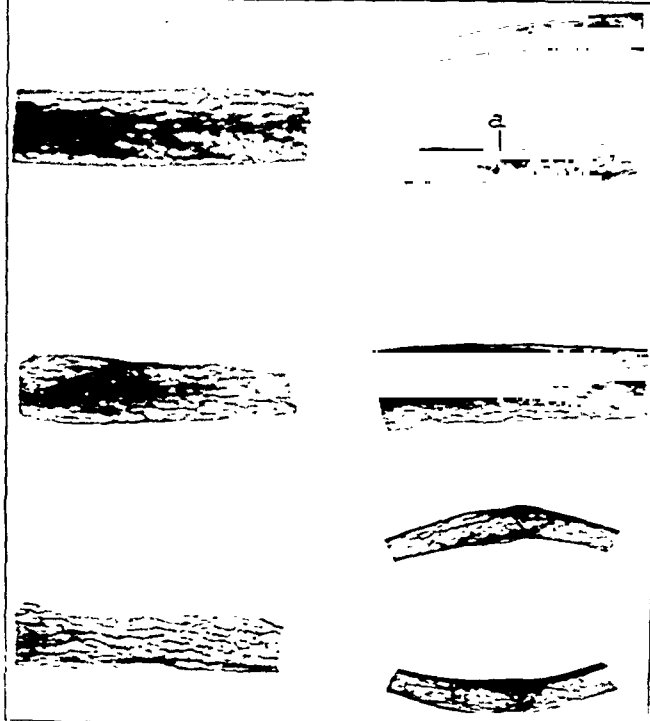


Fig. 10.—Roentgenograms of normal ribs, which demonstrate the two systems of trabeculae: Those of the first are placed longitudinally to the long axis of the rib, and are intersected by those of the second and smaller system, which are transversely situated to the long axis of the rib and which bridge opposing cortical surfaces. Note the thickened cortex in the section cut posterior to the angle of the rib (a).

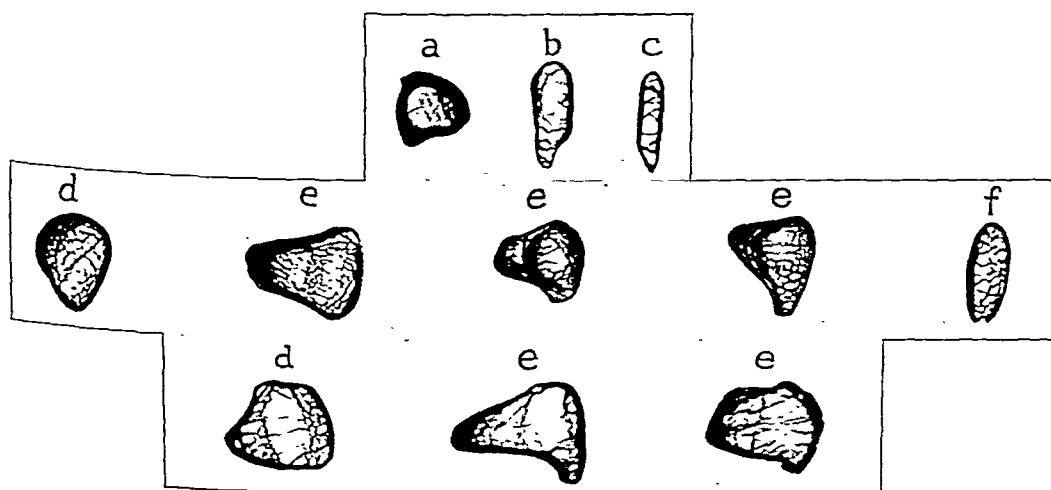


Fig. 11.—Roentgenograms of cross-sections of a normal rib, posterior to the angle of the rib near its vertebral articulation (a) at the angle (b) and at the sternal end (c), and of two transformed ribs posterior to the angle of the rib (d), at the angle (e) and at the sternal end (f). In the latter group note the evidence of greatest deposits of new bone at the angles and progressively diminishing toward both extremities, the absence of new bone at the sternal end and consequently a normal oval contour, the thickened cortex and the increase in trabeculae throughout. The cortex of the section of the normal rib (a) is thicker than that of the transformed ribs (d) because it was cut at a greater distance posterior to the rib angle and nearer its vertebral articulation.

intention. On the eighth postoperative day considerable serosanguineous fluid was aspirated from the subcutaneous tissues. Cultures of it were sterile.

The animal was killed sixty days after operation. The rib segments which had been denuded of periosteum were partially necrotic, and the portion of the mesially displaced periosteum which was in contact with the interposed muscle had produced no new bone. But at the borders of the interposed muscle where the periosteum was in direct contact with neither muscle nor the cortex of the rib from which it had been lifted, a layer of new bone had been deposited on the rib, between its cortex and the periosteum. A cross-section of one of these ribs at this site (fig. 6B) presents a picture almost identical with that observed in experiment 1 (fig. 6A). Consequently its histologic changes need no further comment.

It is apparent that the same physiologic response of the rib and its periosteum has been produced experimentally by two widely divergent methods. In experiment 1 there was a response to aseptic inflammation of foreign body reaction and in experiment 2 a response to traction on and separation of periosteum from bone.

#### COMMENT

In an endeavor to correlate these clinical and experimental observations and to explain the cause and nature of the transformation observed in these ribs two physiologic processes or principles will be considered. These may be designated as the osseous and periosteal response to (1) inflammation, periostitis or osteoperiostitis and (2) functional demands (Wolff's law<sup>3</sup>).

*Inflammatory Response.*—The intimate relation of the inflamed and infected parietal pleura to the adjacent surfaces of the overlying ribs and periosteum with their respective lymphatic communications makes a certain degree of secondary periostitis or osteoperiostitis almost inevitable. As observed in case 1, this inflammatory reaction is manifested by a marked periosteal and subperiosteal cellular proliferation (fibroblasts and osteoblasts) and the deposition on the old cortex of trabeculae of new bone with cellular and fatty marrow spaces enclosed in a newly formed cortex of dense bone. This process may be repeated several times to form tiers of cancellous bone separated by layers of dense bone. From this picture one gains the impression that there have been repeated stimuli to osteogenesis, and to each a reproductive

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3. Wolff, J.: Das Gesetz der Transformation der Knochen, Berlin, A. Hirschwald, 1892; Ueber die Wechselbeziehungen zwischen der Form und der Funktion einzelnen Gebilde des Organismus, Leipzig, F. C. W. Vogel, 1901; Die Lehre von der funktionellen Pathogenese der Deformitäten, Arch. f. klin. Chir. 53:831, 1896; The Law of Transformation of the Internal Architecture of Bones in Pathological Changes of the External Form of the Bone, Sitzungsab. d. K. Pr. Akad. d. Wissensch., Berlin 1:475, 1884.

response. In figure 2 *A*, there may be discerned three separate strata or attempts at new rib formation.

This same architectural arrangement of spongy and cortical new bone and its deposition in layers is observed frequently in subperiosteal new bone formation in long bones (Kauffmann<sup>4</sup>). Likewise an analogous condition occurs not infrequently in an extremity in which there is a cellulitis with the infection superficial to the periosteum. The periosteum takes part in the regional inflammatory reaction, and the ensuing osteogenic response produces a histologic picture of newly deposited bone precisely the same as that observed in the rib specimens which were in contact with the infected parietal pleura. I recently studied two such specimens, both obtained from the external surface of the tibia.

The significance of fibrous replacement of the normal cellular and fatty marrow of the old bone of two of the rib specimens (figs. 3 and 5) and of its calcification in the one instance (fig. 3 *B*) is somewhat problematic. Since these pathologic changes elsewhere in the body, excepting metabolic disturbances and new growths, occur in tissues of low vitality which have been the seat of chronic low grade infection or in tissues which have undergone necrosis, it is reasonable to interpret them as evidence of degeneration. Brunschwig<sup>5</sup> has reported the occurrence of calcified fibrous bone marrow in three cases of chronic osteomyelitis of over fifty years' duration. In two of the cases it occurred only in dead bone which had been sequestered or which was undergoing sequestration, but in the third case there was calcification in fibrous marrow of living bone some little distance from a large osteomyelitic cavity. He<sup>6</sup> also reported the observation of extensive calcification in the dense fibrous lining of an old bone cyst. Phemister<sup>7</sup> has noted its occurrence in tuberculous sequestrums. It is of interest that Brunschwig, in an extensive search of the literature, could find no record of similar observations.

To make deductions by analogy from this small amount of data would be absurd. However, the possibility of preexistent low grade nonsuppurating osteomyelitis of these two ribs with subsequent fibrosis and calcification is suggested. That these changes occurred principally in the marrow nearest the infected empyema cavity may have similar significance.

4. Reimann, in Kauffmann: *Pathology for Students and Practitioners*, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2.

5. Brunschwig, A.: *Epithelization of Bone Cavities and Calcification of Fibrous Marrow in Chronic Pyogenic Osteomyelitis*, *Surg., Gynec. & Obst.* **52**: 759 (March) 1931.

6. Brunschwig, A.: *Solitary Bone Cysts of Long Duration*, *J. Bone & Joint Surg.* **12**:141, 1930.

7. Phemister, D. B.: *Necrotic Bone and the Subsequent Changes Which It Undergoes*, *J. A. M. A.* **64**:211 (Jan. 16) 1915.

From the observations of Cullmann,<sup>8</sup> Wolff obtained the third principle involved in his law. While observing an anatomic exhibit prepared by von Meyer, Cullmann, a Viennese mathematician, was impressed with the remarkable resemblance existing between the internal bony architecture of the head, neck and shaft of the normal human femur and the graphostatic diagram of a Fairbairn crane. By applying a load of 30 Kg. (the approximate load borne by an adult human femur) to the crane and by projecting the resultant lines of force, he was able to demonstrate a definite analogy in the courses of the trabeculae of the head and neck of the femur as seen in the frontal section and in those of the trajectories of his diagram. He concluded that bone was constructed in accord with mechanical principles to provide the greatest strength and efficiency with a minimum of material.

In a subsequent investigation of a large number of bones which were deformed as a result of abnormal function, trauma and disease, Wolff<sup>23</sup> demonstrated the observance of the same mathematical principles in these reconstructed and transformed bones. Since any change in the external form of a bone is followed by a change in the direction of the forces of traction and pressure acting on it, a transformation of its inner architecture along these lines of force should occur in maintenance of mechanical efficiency. That this does occur, and according to mathematical principles, Wolff demonstrated by determining the changes mathematically before verifying them anatomically. Apparently trabeculae which have been rendered statically useless by a change in the form of the bones are destroyed and are replaced by new trabeculae adjusted to the changed form.

From a very laborious study Koch<sup>10</sup> calculated the forces of weight-bearing in all their components acting on each system of trabeculae of the femur at various levels, and determined the relative factors of safety at these levels. From these calculations he was able to predict with a high degree of accuracy the relative frequency of fractures at various levels when forces acting along their normal axes were increased beyond the factor of safety.

Gallois and Japiot<sup>24</sup> studied the inner bony structure of vertebrae (predominantly spongy bone) and arrived at conclusions confirmatory of Wolff's law. From a roentgenographic study of femora of various species of animals, Freiberg<sup>25</sup> demonstrated a variance of architecture consistent with the variation in function.

23. Wolff, J.: Bemerkungen zur Demonstration von Roentgenbildern der Knochenarchitectur, Berl. klin. Wchnschr. **37**:381, 1900.

24. Gallois and Japiot: Architecture intérieure des vertèbres, Rev. de chir. **63**:688, 1915.

25. Freiberg, A. H.: Wolff's Law and the Functional Pathogenesis of Deformity, Am. J. M. Sc. **124**:956, 1902.

It is reasonable to assume that the bony architecture of the ribs has been constructed on the same mechanical principles as all other bones, and that every change in the forms and functions or functions alone would result in changes in internal architecture and external conformation. The complexity of the functions for which ribs are designed makes an analysis of the forces acting on them and a projection of those forces impossible. The stresses of superincumbent weight have little importance compared to the muscle pull of respiratory excursions and the stress incident to the unequal pressures on the internal and external surfaces of the ribs during the inspiratory phase of respiration. Likewise, these forces are distributed over a large area and are shared to a small extent by other structures such as the vertebral column. Unquestionably, the bony thoracic cage possesses a large factor of safety for the protection of the enclosed viscera against external violence. Equally uncertain are the appraisal and analysis of the alteration of forces of stress, compression and torsion resulting from a chronic infection of the pleural cavity. In the acute stage of the disease the affected side usually is splinted by spasm of the muscles not only of the hemithorax but also of the abdomen, back and neck of the same side. With progression to chronicity and in the process of healing the pleural scar contracts and exerts increased and abnormal forces on the overlying ribs.

In accord with Wolff's law a transformation of the costal bony architecture to meet these abnormal forces would be expected, and the transformed ribs would represent functional rather than pathologic deformities. In an endeavor to investigate the changes of the inner architecture of these abnormal ribs as compared to the normal, microscopic and roentgenographic studies of sections cut in transverse, longitudinal and sagittal planes were made. As illustrated in figures 9A and 10 the cancellous structure of the normal rib consists of two principal systems of trabeculae. The larger and thicker trabeculae traverse for long distances the long axis of the rib. They leave the cortex at rather acute angles, and at the angle of the rib they appear to cross the cancellous space and join the opposite cortex (probably to buttress this segment which receives greatest stress). The second or smaller system is composed of short trabeculae placed roughly at right angles to the long axis of the rib. Since these trabeculae irregularly intersect those of the longitudinal system to produce a honey-comb structure, it is impossible definitely to trace their courses, but it would appear that they tend to bridge opposing cortical surfaces. Posterior to its angle each rib, with the exception of the first, becomes somewhat more round in contour. The cortex is much thicker and the spongiosa contains comparatively few trabeculae. This fact and the stratified composition of the cortex of some ribs (fig. 4) add support to the



contention of von Meyer and Wolff that the cortex of all bones is made up from a condensation of the peripheral portions of the trabeculae of the spongiosa.

The inner architecture of the abnormally shaped ribs presents definite changes. The longitudinal trabeculae are increased in numbers and show marked peripheral condensation to form a relatively thick but loosely packed cortex (figs. 2 *B* and 9 *B*).

The occurrence and significance of fibrous replacement of normal marrow and of calcified fibrous marrow have been discussed. Similarly the subperiosteal deposits of new bone have been dealt with. To explain the changes in the marrow on the basis of a purely functional response is impossible. The subperiosteal new bone may in part represent a transformation in accordance with Wolff's law. Although much evidence, already enumerated, indicates that the periostitis or inflammatory response initiates osteogenesis, subsequent stimuli may come from contraction of the pleural scar.

Experiment 2 was designed to determine this response of periosteum and bone to tension on the periosteum and its separation from the bone. New bone was laid down in precisely the same manner as occurred in response to inflammation in experiment 1 and as has been observed in the human specimens. From the results of this experiment it may be deduced that tension from contraction of the pleural scar of chronic empyema may initiate secondary stimuli to osteogenesis and deposition of the younger tiers of subperiosteal new bone, as illustrated in case 1 (fig. 2*A*).

#### SUMMARY AND CONCLUSIONS

1. The structural changes commonly observed in ribs which overlie empyema cavities and the relation of these changes to the parietal pleura are described.

2. A report of an investigation and certain deductions relative to the pathogenesis of these changes are presented. This analysis, based on clinical, histologic, roentgenographic and experimental data, indicates that the transformation has been brought about by the action of two physiologic processes.

The first of these, the inflammatory response or periostitis which probably is most active during the acute stage of an empyema, occurs in that portion of the rib and its periosteum which is in contact with the dilated intercostal vessels and the inflamed and infected parietal pleura and causes the laying down of one or more distinct layers of subperiosteal new bone. Further evidence of a secondary inflammatory response and possibly of infection may be deduced from the presence in two rib

specimens of fibrous and calcified fibrous bone marrow. These degenerative changes suggest the possibility of a preexistent osteitis or osteomyelitis.

The second factor has been designated as a functional response in which the osteogenic elements of these ribs bring about certain transformations in accord with the principles outlined in Wolff's law. It is probable that the proliferation of trabeculae and their peripheral condensation to form the thickened cortex observed in the transformed ribs represent a functional response to certain abnormal forces acting on the ribs as a result of contracture of the pleural scar of the underlying empyema. Likewise, this same physiologic process may be in part responsible for the subperiosteal deposits of new bone.

It would appear that the greatest abnormal force acting on these ribs overlying chronic empyema cavities is the centripetal traction of the contracting pleural scar. To resist this force the transformation of the inner architecture constantly observed in the specimens examined would logically be anticipated.

Dr. John Alexander permitted the use of his collection of pathologic ribs in this study. Dr. C. V. Weller and Dr. J. C. Bugher assisted in the preparation of the pathologic specimens.

# COMBINATION AVERTIN-ETHER RECTAL ANESTHESIA

## EXPERIMENTS ON ANIMALS

GEORGE HALSEY HUNT, M.D.

RED BANK, N. J.

The purpose of the experiments here described was twofold: first, to determine whether a combination of avertin (tri-bromethanol) and oil-ether, administered by rectum in experiments on animals, would produce anesthesia measurably deeper or more lasting than avertin alone; and second, to determine the relative safety of these drugs when thus used. The work was undertaken in the hope of securing a combination of anesthetic effects which would give a safe anesthesia in man with the comfortable, rapid induction characteristic of avertin and the more sustained, deeper anesthesia induced by ether, making supplementary inhalation anesthesia unnecessary for operations for which marked relaxation is not required.

## LITERATURE

The development of tri-bromethanol in Germany and its introduction into this country some years ago have given rise to an extensive literature, originally in German, but more recently in English also. This literature has been well summarized by many American writers, notably by Waters and Muehlberger,<sup>1</sup> who in addition reported experimental and clinical investigations. However, in only one article, by York and Schork,<sup>2</sup> have I found any reference to the use of rectal ether as a supplement to avertin anesthesia. They reported the use of this combination for several patients, with excellent results, but had not done any experimentation on animals with the procedure.

## EXPERIMENTS WITH ALBINO RATS

The first experiments were conducted with albino rats, which have the double advantage of being easy to handle and of having relatively capacious rectums. The technic used was as follows:

No preliminary medication was given. A small amount (from 10 to 20 cc.) of 3 per cent aqueous solution of avertin was prepared just before each group of

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From the Department of Surgery, College of Physicians and Surgeons, Columbia University. This experimental work was done while the author was a Junior Fellow in Surgery.

1. Waters, Ralph M., and Muehlberger, C. W.: Tribromethanol Anesthesia. *Arch. Surg.* **21**:887 (Dec.) 1930.

2. York, Arthur J., and Schork, R. J.: Tribromethanol as a Basal Anesthetic. *South. M. J.* **24**:244, 1931.

experiments and kept at 40 C. over a water bath. For each animal the dose of avertin was calculated from the body weight, and the corresponding quantity of 3 per cent avertin solution was measured into a syringe and injected into the rectum through a  $2\frac{1}{2}$  to 3 inch segment of a small rubber catheter. Care was used to have the lumen of the catheter filled with solution, so that all of the

TABLE 1.—*Experiments on Albino Rats with Avertin Alone, with Avertin-Ether and with Ether Alone*

Avertin in Gm. per Kg.	Ether in Cc. per Kg.	Number of Rats	Length and Depth of Anesthesia and Result
0.15	..	2	Drowsiness only; recovery for both
0.3	..	7	1 rat, complete anesthesia for $1\frac{1}{2}$ hours, recovery 6 rats, drowsiness and partial anesthesia, all recovered
0.5	..	2	1 rat, anesthesia for 3 hours, recovery 1 rat, anesthesia for 5 hours, recovery
0.6	..	2	1 rat, anesthesia for 1 hour, recovery 1 rat, anesthesia for 3 hours, recovery
0.7	..	2	1 rat, death after $\frac{1}{2}$ hour 1 rat, anesthesia for 2 hours, recovery
0.3	1	4	1 rat, death after $1\frac{1}{2}$ hours 1 rat, partial anesthesia for 1 hour 1 rat, complete anesthesia for 1 hour 1 rat, complete anesthesia for 2 hours
0.3	2	5	1 rat, death after 20 minutes 1 rat, anesthesia for 1 hour 1 rat, anesthesia for $1\frac{1}{2}$ hours 2 rats, anesthesia for $2\frac{1}{2}$ hours
0.3	4	5	1 rat, death after 50 minutes 1 rat, anesthesia for 2 hours 3 rats, anesthesia for 3 hours
0.3	5	6	5 rats, in 2, death after $4\frac{1}{2}$ or 5 hours; 3 found dead in the morning; in 3 of the 5 signs of recovery at one time or another 1 rat, anesthesia for $4\frac{1}{2}$ hours, recovery
0.3	6	1	1 rat, death after 2 hours
0.4	5	2	2 rats, death; one after 10 minutes; one after 3 hours
0.4	10	2	2 rats, death after 3 or $3\frac{1}{2}$ hours
...	2	1	1 rat, partial anesthesia
...	4	3	3 rats, partial anesthesia
...	8	2	1 rat, death during night 1 rat, partial anesthesia only
...	10	4	1 rat, anesthesia for $\frac{1}{2}$ hour 3 rats, partial anesthesia only
...	15	2	1 rat, death during night 1 rat, partial anesthesia only

measured quantity was injected. After several methods of holding the rats had been tried, best results were obtained by tying them in the dorsal position to a small animal board. During and after injection, compression of the preanal region against the extended tail prevented escape of the injected solution. The rats were deemed anesthetized when they fell to the cage floor and lay motionless, and anesthesia was assumed to continue until they first made ataxic efforts to regain their feet, or until they responded to painful stimuli, such as application of a Kocher clamp to the skin.

In the experiments in which ether was used, a solution composed of two parts of ether and one part of liquid albolene was made, and the doses were calculated, measured and injected in the manner described. When the avertin-ether combination was used, the avertin was injected first, and the oil-ether from five to ten minutes later, after the animal was anesthetized.

A complete tabulation of these experiments will be found in table 1.

These experiments were not expected to give conclusive proof of either the efficacy or the safety of avertin-ether anesthesia, but were intended merely as preliminary guides in undertaking the more extensive and accurate work on dogs. There was conclusive evidence, however, that doses of avertin and ether which separately induced only partial anesthesia, when given together produced a deep anesthesia lasting from one to three hours; for example, avertin, 0.3 Gm. per kilogram, plus ether, 4 cc. per kilogram.

Because of the mortality, from 20 to 25 per cent, with the smaller doses of this combination, the work with dogs was approached with caution.

#### EXPERIMENTS WITH DOGS

This work involved a good deal of trial and error. In the first twenty-three experiments, the dogs were given no preliminary medication. With several dogs, enemas were used as preanesthetic preparation; others were starved for twenty-four hours; in a third group both methods of preparation were used; in a fourth group, neither.

In these experiments, avertin alone in doses of from 0.1 to 0.3 Gm. per kilogram gave anesthesia lasting from one-half to one hour. Addition of ether in doses of from 1 to 2 cc. per kilogram slightly increased the length of anesthesia though the maximum duration obtained was one hour and twenty minutes (with avertin, 0.3 Gm. per kilogram, plus ether, 2 cc. per kilogram); but the majority of these experiments were unsuccessful because of expulsion of the oil-ether mixture either immediately or after some minutes. In an effort to overcome this difficulty, ether was emulsified with milk and injected; and in another case a solution was made by dissolving the calculated amount of avertin in the calculated amount of oil-ether mixture. Both of these procedures failed; the ether-milk mixture was expelled as promptly as the oil-ether, and the avertin-oil-ether solution produced only drowsiness.

At Dr. Gwathmey's<sup>3</sup> suggestion, a preliminary medication of morphine, 10 mg. per kilogram, was then instituted, as recommended by Beckman.<sup>4</sup>

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3. Gwathmey, James T.: Personal communication.

4. Beckman, Harry: On the Alleged Synergism of Magnesium Sulfate and Morphin When Injected Prior to the Induction of Anesthesia by the Oil-Ether Colonic Method, *J. Lab. & Clin. Med.* **10**:189, 1924; Colonic Anesthesia in Dogs, *J. Am. Vet. M. A.* **20**:67, 1925. (This gives a somewhat more complete description of the technic than appears in his other article.)

## FINAL TECHNIC

The technic ultimately worked out was as follows:

Enemas and starvation were dispensed with. One hour before the injection of avertin, the dog was weighed, and 10 mg. of morphine sulphate per kilogram of body weight was injected subcutaneously. The kilogram dose of avertin having been decided on, the amount of avertin fluid to be used was calculated from the body weight. (Avertin fluid is a 100 per cent solution of avertin in amylene hydrate.) From the figure thus obtained, the amount of distilled water necessary to make a 3 per cent solution of avertin was calculated. This quantity of distilled water was heated to 40 C., and the avertin was added from a 5 cc. pipet graduated in 0.1 cc. The mixture was agitated until solution was complete, and immediately injected.

With the dog held on his side by an assistant, a 30 French soft rubber catheter was inserted from 7 to 10 inches into the rectum. To the free end of the tube was attached a glass syringe with a capacity of about 30 cc., and with a tapering nozzle which fitted snugly into the tube. This syringe was used as a funnel; the rubber bulb was used merely to start the flow and to overcome any mechanical blockage, such as feces, in the orifice of the tube; the fluid was allowed to run in by gravity, with the syringe held not more than a foot higher than the anus.

If only avertin was being given, the tube was withdrawn as soon as all the fluid had been injected; if ether was to be injected, the tube was left in place and clamped, and after an interval of from ten to twenty minutes, the syringe was filled with oil-ether, the clamp removed, the injection completed, and the tube withdrawn. In one case, when anesthesia of long duration was required, the tube was left in place after injection of the first dose of ether; four hours later, when the dog began to move, a second dose of ether was injected, with prompt deepening of the anesthesia.

The ether solution used for these experiments was made up fresh for each dog; the calculated amount of ether was measured out, and half that amount of albolene was added. The mixture was not heated, but was shaken to insure thorough mixing, and injected at room temperature.

The addition of morphine to the technic obviated what had previously been the most serious difficulty, namely, forcible expulsion of the oil-ether mixture; but with the larger quantities of solutions injected there was frequently a leakage through the relaxed anus. This could be fairly well controlled by pressure on a folded gauze pad placed over the anus; if a tendency to leakage persisted more than a few minutes, pressure was continued by leaving the pad in place, pulling the tail forcibly forward between the legs, and clamping the hair of the tip of the tail to the hair of the abdomen.

Anesthesia was considered to have begun as soon as the dogs fell asleep, usually from three to five minutes after the injection of avertin. It is true that surgical anesthesia does not begin as soon as a dog falls asleep, but only after an interval of from ten to twenty minutes of deepening narcosis; as stimulation during this period is known to hinder and delay the development of deep narcosis, it was assumed that less error would be introduced by taking the time when the dogs fell asleep than by determining the actual onset of surgical anesthesia by repeated painful stimuli.

Anesthesia was considered to continue until application of a Kocher clamp to the skin of the flank evoked a definite response. The first response was usually a lifting and turning of the head toward the clamped flank. The movement was

uncertain and slow, and the effort was usually abandoned after a second or two. Occasionally, dogs began to move spontaneously before they responded to the clamp; in these cases, the time that movement began was considered to mark the end of anesthesia. In actual operation, supplemental anesthesia would not be required for some time after this point, as the dogs remained stuporous for a considerable period, particularly after the larger doses, and in a few instances relapsed into complete anesthesia from which painful stimuli did not arouse them.

*Comment on Technic.*—Adoption of this technic resulted in immediate success. Ether was retained almost invariably (expelled twice in twenty-six experiments), and increasing doses up to a maximum of 9 cc. per kilogram were successfully given.

An interesting question raised by the use of this large dose of morphine was whether in the presence of such a stupefying dose any subsequent procedures could lead to valid conclusions.

One fact pointing toward the affirmative answer was that an hour after injection of morphine, the dogs, though decidedly sleepy, could easily be aroused, and seemed only slightly more narcotized than many human patients who have had ordinary preoperative medication.

I took as the final criterion the pragmatic test, and found that, except in the higher ranges, increases in dosage of avertin or ether, or both, caused fairly constant increases in the duration of anesthesia.

Beckman, using oil-ether rectal anesthesia in dogs, with and without morphine, also concluded that morphine in this dosage does not invalidate the results.

In connection with the injection of morphine, it is of interest that while salivation was fairly common, vomiting or defecation was the exception rather than the rule, even in dogs that were receiving morphine for the first time.

*Results with Small Doses.*—Having overcome the difficulty caused by expulsion of the ether solution, I carried out a group of experiments using small quantities of avertin (0.1 Gm. per kilogram), followed either by no ether or by ether in doses of from 1 to 2 cc. per kilogram (see table 2).

These experiments demonstrated that addition of ether in doses of 1 cc. per kilogram produces a slightly but definitely longer period of anesthesia than avertin alone, and that a dose of 2 cc. of ether per kilogram causes a marked prolongation. Five dogs received this dose, i. e., avertin, 0.1 Gm. per kilogram, followed by ether, 2 cc. per kilogram. The minimum length of anesthesia obtained was one and three-quarter hours; the maximum three and one-half. It is of interest that the dog which remained anesthetized for three and one-half hours was subjected to a gastric resection and bilateral vagotomy, the operation lasting two and three-quarters hours. During the last hour of the operation, the dog made occasional slight movements, but supplemental anesthesia was not required, and ten minutes after the close of the operation he did not respond to a Kocher clamp applied to the flank.

*Margin of Safety.*—After this combination rectal anesthetic had been demonstrated to produce in dogs a measurably longer period of anesthesia than avertin alone, determination of the margin of safety

was next in order. For this purpose I took three dogs which had been used in previous experiments, one of them many times, and gave to one increasing doses of avertin alone; to the second, increasing doses of ether with a constant preliminary dose of avertin, and to the third, increasing doses of both avertin and ether. The results obtained are shown in table 2.

*Lethal Dose.*—There were no fatalities. The nearest approach to a lethal dose was avertin 0.9 Gm. per kilogram. In this case the dog was deeply anesthetized at midnight, thirteen hours after the administration of avertin, with greatly depressed respiratory and cardiac rates (respiration, 10; heart rate, from 42 to 46 per minute). At 8 a. m.

TABLE 2.—*Experiments on Dogs with Morphine (10 Mg. per Kilogram), with Avertin and with Avertin-Ether*

Avertin in Gm. per Kg.	Ether in Cc. per Kilogram									
	0	1	2	3	4	5	6	7	8	* 9
0.1	$\frac{1}{2}$ $\frac{1}{2}$ $1\frac{1}{4}$ $1\frac{1}{4}$	$\frac{1}{2}$ $\frac{3}{4}$ $1\frac{3}{4}$ 2	$1\frac{1}{4}$ 2 $2\frac{1}{2}$ 3 $3\frac{1}{2}$	2 $2\frac{1}{2}$	3 $4\frac{1}{2}$	4 $4\frac{1}{2}$ 6 (divided dose)	..	..	$3\frac{1}{2}$	7
0.2	$2\frac{1}{4}$	..	..	..	3	..	..	..	..	..
0.3	2	..	..	..	..	5	..	..	..	..
0.4	$3\frac{1}{4}$	..	..	..	..	..	$6\frac{1}{2}$	..	..	..
0.5	4 6 $7\frac{1}{2}$ $4\frac{1}{2}$	..	..	..	..	6	..	$4\frac{1}{2}$	..	..
0.6	$4\frac{1}{2}$	..	..	..	..	..	..	..	5	..
0.7	$4\frac{1}{2}$ $5\frac{1}{2}$	..	..	..	..	..	..	..	..	..
0.8	$5\frac{1}{2}$	..	..	..	..	..	..	..	..	..
0.9	13-20 (see text)	..	..	..	..	..	..	..	..	..

Figures represent duration of anesthesia in hours.

the next day he was rolling around the cage in a groggy and uncoordinated manner. This depressed mental and physical condition persisted all day, but on the following morning he was alert and active, and seemed completely recovered. The dogs which received avertin plus ether showed no alarming respiratory or cardiac depression, and when the experiments were stopped because the volume tolerance of the dogs' rectums had just about been reached, the doses seemed to be well below the lethal amounts.

*Ether in Divided Doses.*—In one instance, when anesthesia was required for a long blood-clotting experiment, I gave ether in divided doses, with good results. The dog was anesthetized with avertin, 0.1 Gm. per kilogram, plus ether, 3 cc. per kilogram. At the end of four hours, the anesthesia was beginning to wear off, but injection of an



additional 2 cc. of ether per kilogram caused prompt deepening of the anesthesia, which lasted for two hours more.

*Comment on Results.*—The inconstancy of the results with very large doses may be accounted for in two ways. In the first place, the actual quantities of fluid required are tremendous, compared to the size of the dog. For instance, the dog which received avertin, 0.6 Gm. per kilogram, and ether, 8 cc. per kilogram, weighed 14.4 kilograms. Consequently he was given 4.3 cc. of morphine sulphate solution, 288 cc. of avertin solution and 173 cc. of oil-ether mixture. The magnitude of these figures (461 cc. injected rectally into a dog weighing 14.4 kilograms) may best be realized by multiplying both figures by five; that is, this is equivalent to giving a 2,300 cc. retention enema to a 72 kilogram (158.4 lb.) adult human being. In these ranges, there is naturally some leakage, even with compression of the anal region; this particular dog lost a quantity of avertin solution estimated at 15 cc. (a little over 5 per cent of the total amount injected) and about 5 cc. of the ether solution (about 3 per cent). Leakages in the other experiments were of about the same magnitude.

The more important factor, I believe, was the tolerance acquired by the dogs to morphine and, possibly, to avertin. Previous experimentors have concluded that avertin given repeatedly neither produces tolerance nor has a cumulative effect. My results agree with the latter, and the former is certainly not disproved, in view of the well known fact that tolerance to morphine is readily produced. I did not perform the critical experiment of habituating a dog to morphine and then giving him avertin.

I did, however, wish to check my results with the larger dosages on fresh dogs. Two dogs were obtained which had never been subjected to avertin, and after the usual dose of morphine, were given avertin, 0.5 Gm. per kilogram. The anesthesia obtained lasted six hours in one dog and seven and one-half in the other, as compared with four hours in the habituated dog. One of these dogs was then given avertin, 0.7 Gm. per kilogram, with anesthesia lasting only four and one-half hours, as against five and one-half hours in the habituated dog. The other was given avertin, 0.5 Gm. per kilogram plus ether 5 cc. per kilogram. Anesthesia in this case lasted six hours.

These four experiments gave definitely inconstant results, and raised the question whether the colonic distention caused by these large quantities of fluid does not introduce error by preventing absorption of a good proportion of the injected drugs. At any rate, these doses seem well within the fatal limits.

One additional factor which may have had a bearing on the lack of uniformity when different dogs were used is that larger dogs seem to be more affected by the preliminary morphine, and possibly also by the other drugs.

Typical protocols follow :

Experiment 105, 2-26-32

Dog 536	10 Kg.	Morphine, 10 mg. per Kg. Avertin, 0.1 Gm. per Kg. Ether, 5 cc. per Kg.
12:25 p.m.	Morphine injected	
2:10	Avertin injected	
2:13	Asleep	
2:27-2:30	Ether injected; 5 cc. $\pm$ lost	
3:00	Deep anesthesia	
3:30	Deep anesthesia	
3:50	Deep anesthesia	
4:10	Deep anesthesia	
4:30	Deep anesthesia	
5:00	Deep anesthesia; drawing up of hind legs with each inspiration	
5:20	Same	
5:35	Same	
5:55	Same	
6:10	Same	
6:25	Same	
6:35	Rouses at noise; slow response to Kocher	

Anesthesia for  $4\frac{1}{3}$  hours

Experiment 112, 3-11-32

Dog 447	13.8 Kg.	Morphine, 10 mg. per Kg. Avertin, 0.4 Gm. per Kg. Ether, 6 cc. per Kg.
10:35 a.m.	Morphine injected	
12:12-12:15	Avertin injected	
12:15	Asleep	
12:23-12:31	Ether injected; 10 cc. $\pm$ lost	
12:25	Deep anesthesia	
2:00	Deep anesthesia	
3:05	Deep anesthesia	
4:15	Deep anesthesia	
5:00	Deep anesthesia	
5:35	Deep anesthesia	
6:00	Deep anesthesia	
6:20	Deep anesthesia	
6:30	Deep anesthesia	
6:50	Slow and feeble response to Kocher	

Anesthesia for  $6\frac{1}{2}$  hours

*Autopsy.*—The three dogs which had been used for the increasing dosage experiments were killed, and autopsies were performed. One of these animals had had twelve injections of avertin without morphine and twelve injections with morphine in the course of eleven months. The other two dogs had been used fourteen and ten times, respectively.

In no case were gross lesions found in the liver, kidneys or rectum. Microscopic sections were made of these organs in all three dogs. I could find no histologic lesions in any section, nor could Dr. A. Purdy Stout of the department of surgical pathology.

## COMBINATION ANESTHESIA IN OPERATIONS ON THE DOG

Combination avertin-ether rectal anesthesia can be used to advantage in certain surgical procedures on the dog, particularly for long operations or experiments. I used it successfully for two abdominal operations, one bronchoscopy and one long experiment in blood-clotting. Avertin alone (from 0.1 to 0.2 Gm. per kilogram), with preliminary morphine medication, is undoubtedly sufficient for bronchoscopies and other procedures requiring comparable depth and duration of anesthesia.

The advantages of avertin-ether rectal anesthesia are: (1) the length of anesthesia induced by small doses, (2) the fact that no inhalation anesthesia is necessary and (3) the typically smooth course of the anesthesia, with no struggling and little or no salivation.

The dose recommended for routine administration is avertin 0.1 Gm. per kilogram, followed by ether, from 2 to 3 cc. per kilogram, given according to the technic outlined.

Disadvantages of this anesthesia in dogs are: 1. The dog must be weighed and morphine injected from one and one-fourth to one and one-half hours before the operation is to be begun. 2. The anesthetic solutions must be made up carefully and injected from twenty to thirty minutes before the operation. 3. Morphine and, particularly, avertin are expensive drugs. While these factors will preclude routine use of this anesthesia in most laboratories, I feel that it has a field of definite usefulness.

There were two failures in giving this anesthesia for operations. In one case, the dog had colitis due to distemper, which I should have considered a definite contraindication, except that the distemper in his respiratory tract made inhalation anesthesia seem even less feasible. In this dog, the usual doses produced no anesthesia at all. In the other dog, anesthesia was successful until the operator exposed and manipulated the nerves in the region of the knee joint. The anesthesia was not deep enough for this procedure, and ether inhalation had to be instituted.

## COMBINATION ANESTHESIA IN SURGICAL PROCEDURE ON MAN

I have had no clinical experience with this combination. York<sup>5</sup> has used it in over one hundred cases, including a number of thoracoplasties, and reports in a personal communication a lower mortality than he would expect in a similar group of cases with other anesthetic agents. He gives the usual dose of avertin (from 60 to 100 mg. per kilogram), and follows this with from 30 to 60 cc. (1 to 2 ounces) of ether. He

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5. York, Arthur J.: Personal communication.

has also given ether in divided doses with success. Further cautious clinical trial seems warranted, in view of the experience of York and Schork and of the experimental work here presented.

#### SUMMARY

In albino rats, rectal injections of avertin followed by oil-ether gave a definitely longer period of anesthesia than avertin alone.

Similar procedures were carried out in dogs, and a successful technic evolved. As in rats, the combination of avertin and ether gave a longer period of anesthesia than avertin alone.

The margin of safety seemed to be wide. No dog died, in spite of doses at least three times as large as the effective anesthetic dose, which is considered to be avertin, 0.1 Gm. per kilogram, followed by ether, from 2 to 3 cc. per kilogram.

Autopsies on three dogs which had been subjected to many anesthetics failed to reveal any gross or microscopic pathologic condition in the kidneys, liver or rectum.

This combination anesthesia is recommended for use in surgical procedure on dogs in selected cases. Its use in man, as advocated by York and Schork, is considered.

#### CONCLUSIONS

1. In the dog, combination avertin-ether rectal anesthesia gives a definitely longer period of anesthesia than avertin alone; the procedure is safe; the lethal dose is at least three times the effective anesthetic dose. The clinical experience of York and Schork is thus corroborated experimentally.

2. On the basis of both clinical and experimental experience a wider clinical use of this combination anesthesia seems advisable.

# FIFTY-FIRST REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from page 816)

## OSTEOMYELITIS

*Acute Osteomyelitis in Children.*—Statistics from eight British hospitals supported Wakeley's<sup>25</sup> contention that acute osteomyelitis was a disappearing disease. He suggested that the decrease of incidence was due to better hygiene and the earlier removal of possible septic foci. He questioned the general belief that trauma played an important part in the causation of the disease. Early drainage was indicated in all cases, a trephine being used at first in the juxta-epiphyseal diaphysis. The efficacy of multiple drill holes as a means of instituting drainage was doubted. In late cases, in which the whole of the diaphysis was involved in the disease, diaphysectomy followed by bone grafting was advised. Fixation of the limb was considered to be necessary to rest the inflamed bone and eliminate pain.

## CHRONIC ARTHRITIS

*Treatment of Chronic Arthritis of the Spine.*—Swaim and Kuhns<sup>26</sup> discussed the treatment of atrophic arthritis of the spine. Five essentials of treatment were considered: (1) early diagnosis, (2) arrest of the general disease as quickly as possible, (3) improvement in the motion of the ribs, (4) correction of the forward droop of the spine and (5) improvement of the patient's general health.

25. Wakeley, C. P. G.: Brit. M. J. 2:752, 1932.

26. Swaim, L. T., and Kuhns, J. G.: Arch. Phys. Therapy 13:517, 1932.

Permanent cure came only slowly. The rapid improvement sometimes seen with the use of drugs or vaccines was usually not permanent. Important measures, such as proper diet, intestinal regulation, endocrine therapy (occasionally) and correction of faulty body mechanics, needed to be followed for many months to have a permanent beneficial effect. Emphasis was placed on the importance of increasing vital capacity and the respiratory expansion of the ribs. Without this expansion of the ribs, death from pneumonia was frequent. Rest was an important factor in conquering the disease. Restoration of the normal curves of the back and improvement in general body mechanics was brought about by exercises, and a gradual correction of the forward flexion of the spine by means of supporting plaster shells and bed positions. No rapid corrections or manipulations were attempted. Improvement in the position of the spine and thorax was accompanied by improvement in the patient's general health and resistance. Patients were kept in bed until all pain and muscle spasms had subsided. Gentleness was the keynote of all therapeutic exercises. Involvement of the hips presented the serious and intractable features of the disease. Once the arthritis had become firmly established in the hip, it usually went on to ankylosis, and little could be done except to prevent deformity.

#### CIRCULATORY DISTURBANCES OF THE EXTREMITIES

*General Care of Peripheral Vascular Disease.*—Reid<sup>27</sup> stressed certain practical points in the care of peripheral vascular disease and emphasized particularly the importance of intelligent cooperation on the part of the patient in carrying out treatment of these conditions. The position of maximum circulation for the affected part should be determined in each case. Too much elevation often encouraged the development of gangrene. The necessity of keeping the skin soft and the extremity warm, and the avoidance of trauma were mentioned. The Buerger exercises carried out consistently and the maintenance of an adequate fluid intake were recommended. The author advised doing amputations between two tourniquets in cases of infected or gangrenous extremities.

[ED. NOTE.—The article is well written and practical; while containing nothing particularly new, it does summarize well the important points in the care of these patients. It should be read by all physicians interested in surgery of the extremities.]

*Quantitative Determination of Vasoconstrictor Spasm.*—Morton and Scott<sup>28</sup> emphasized that before a decision is made as to the type of

27. Reid, M. B.: Ann. Surg. 96:733, 1932.

28. Morton, J. J., and Scott, W. J. M.: Ann. Surg. 96:754, 1932.

treatment to be applied in a particular case of peripheral vascular disease, it is first necessary to determine whether the complaint is due to a failure of the blood supply, and secondarily whether this failure is due to organic occlusion or to sympathetic vasoconstriction or to a combination of these. Observations were made on normal persons and on persons suffering from vascular disease to determine the vasodilatation level. They found the most convenient method to be the conduction nerve block. In selected cases, lumbar or cervical sympathectomy was considered advisable, if by the nerve block test it could be established that vasodilatation could be produced, the surface temperature raised and spasm relieved. The establishment of collateral circulation was considered an important result of sympathectomy.

*Sympathetic Ganglionectomy and Trunk Resection in Circulatory Disturbances.*—Mayo and Adson<sup>29</sup> wrote extensively concerning the surgery of the sympathetic nervous system, and reviewed the anatomy, historical facts and the surgical technic of the operative procedures. The operation of sympathetic ganglionectomy as applied to Raynaud's disease, thrombo-angiitis obliterans and scleroderma was presented, and the results in a large series of cases recorded.

[ED. NOTE.—This article gives an excellent summary of the operative procedure and its clinical applications.]

#### BONE AND JOINT SURGERY

*Whitman's Reconstruction Operation on the Hip Joint.*—Lowendorf<sup>30</sup> based his remarks on a study of the end-results in 15 of 18 cases in which the Whitman reconstruction operation had been done. The indications for the operation were: (1) ununited fracture of the femoral neck, (2) old slipped epiphysis, (3) pathologic dislocation of the hip and (4) osteo-arthritis or traumatic arthritis of the hip. The ideal result obtainable was a movable, painless and stable hip. Good results were obtained in 11 of the 15 cases. The operation was done in 8 of these for nonunion of the femoral neck. Good results were obtained in all cases of this type. Operation was performed in the other cases for arthritis. The conditions in the 4 cases in which poor results were obtained were: osteo-arthritis, old suppurative arthritis, generalized arthritis and Charcot's joint. In 14 cases, the average flexion contracture was 14 degrees and the range of flexion 67 degrees, approximately 20 degrees abduction and 20 degrees adduction. Stable hips were obtained in 14 of the 15 cases. Pain was relieved in 12 cases.

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29. Mayo, W. J., and Adson, A. W., *Ann. Surg.* **96**:733, 1932.

30. Lowendorf, C. S.: *Am. J. Surg.* **18**:64, 1932.

## MISCELLANEOUS

*Cerebral Injuries at Birth.*—Phelps<sup>31</sup> advised a careful study of cerebral injury at birth from the social, mental and physical standpoint, before outlining any form of treatment. For the study of the physical side, he found motion pictures of great value. He discussed "dyskinesia" under the headings of (1) spasticity, (2) athetosis, (3) overflow of "synkinesia," (4) incoordination or ataxia and (5) tremor. The principles of treatment were: (1) relaxation, which was very essential before any progress could be made, (2) strengthening exercises and (3) reciprocal motions, to be gained only after relaxation had been accomplished. (4) Active stretching exercises were useless. (5) Surgical intervention should be considered only after the aforementioned preliminary forms of treatment had been tried. The various operative procedures, such as tendon division and nerve resections, were discussed.

*Angle of Gait.*—Morton<sup>32</sup> examined the angle of gait of 147 natives of Central Africa (87 men, 30 women and 30 children), and found that the natural angle of gait was 7.5 degrees of out-toeing. This finding corresponds closely with those of Dougan and Patek, who made similar studies on college men and women, but is contrary to the ideas of some orthopedic surgeons who teach patients that toeing in or walking with feet directly forward is the ideal. The author analyzed the benefits of two functional elements in the mechanics of stride: (1) lateral stability effected by widening the position of the feet, i. e., toeing out, and (2) a forward thrust from behind the moving center of body weight brought about by having the heels placed more closely together.

*Glycine Treatment for Progressive Muscular Dystrophy.*—The creatine-creatinine excretion and the tolerance to creatine were studied by Milhorat<sup>33</sup> in cases of muscular dystrophy. He observed that the feeding of glycine with or without phosphate raised the elimination of creatine in 14 cases of progressive muscular dystrophy. No increase in the elimination of creatine was observed in secondary muscular atrophies. Consequently, the feeding of glycine served as a differential diagnostic measure between primary and secondary degeneration. Under this treatment, the author found rapid improvement in the muscles not seriously atrophied with later less rapid progress. Histologic evidence of muscular tissue from 3 patients was difficult to interpret. Muscular fibers were either quite atrophied or entirely normal. No middle stages were observed.

[ED. NOTE.—An easily available inexpensive source of glycine is gelatin.]

31. Phelps, W. M.: J. Bone & Joint Surg. **14**:773, 1932.

32. Morton, D. J.: J. Bone & Joint Surg. **14**:741, 1932.

33. Milhorat, A. T.: Deutsches Arch. f. klin. Med. **174**:487, 1933.



*Ruptures and Tears of Muscles of the Lower Extremity.*—Fifteen cases of ruptured muscles in the lower extremity were reported by Gilcreest.<sup>34</sup> There was a history of trauma in all the cases. In only 2 was the trauma trivial enough to cause comment: A woman of 35 ruptured the quadriceps femoris tendon while bending over with the knees flexed. Another patient ruptured the plantaris when stepping off a street car. Ruptures of the vastus internus quadriceps tendon, rectus femoris, patellar ligament, semitendinosus, inner head of the gastrocnemius, achilles tendon and plantaris were reported. The author concluded that partial or complete ruptures of the muscles and tendons of the leg occurred more often than was generally supposed. Articular symptoms, particularly in the knee, might mislead one in making a diagnosis. Early surgical repair gave good results. The prognosis was good if proper treatment was given early.

*Pneumoroentgenogram of the Knee Joint.*—With the aid of a pneumothorax apparatus, Schum<sup>35</sup> was able to inject from 60 to 200 cc. of unfiltered air into the knee joint. The joint puncture was usually made under local anesthesia, lateral to the patella, and air was not injected until the operator was sure that the needle was free in the joint. To test this, if there was any doubt, some salt solution was first run through. This was done to avoid air emboli, the major danger in this procedure. The resultant roentgenograms, taken stereoscopically, anteroposteriorly and laterally, were most interesting and often of much clinical value. Especially interesting were pictures taken in lesions of the lateral ligaments. Lesions of the menisci often were recognizable, but findings were used only when positive. In 54 cases clinical and roentgenographic findings pointed to injuries of the meniscus; in 88.7 per cent of these the conditions were found to have been correctly diagnosed when checked at operation. Of the remaining 11 per cent (6 cases), the diagnosis in 3 cases was indicated in any event by the demonstrable presence of free bodies and injuries to the fat pad, while in 3 cases pneumoroentgenography definitely failed to be of value. No trouble was encountered in performing the injection of air 114 times on 98 patients. A sense of fulness was usually experienced when the joint was properly filled, but no general symptoms appeared. The needle was left in place during the taking of the roentgenograms to avoid subcutaneous emphysema. After roentgen exposures were completed, the air was gently massaged out. Some clinical improvement was noted in some cases simply as a result of the distention.

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34. Gilcreest, E. L.: Ruptures and Tears of Muscles and Tendons of Lower Extremity: Report of Fifteen Cases, *J. A. M. A.* **100**:153 (Jan. 21) 1933.

35. Schum, H.: *Deutsche Ztschr. f. Chir.* **238**:1, 1933.

*Osteochondritis Necroticans "Findens" (Divided) of the Sesamoid Bone of the First Metatarsal.*—Kimmelstiel and his co-workers<sup>36</sup> presented a careful study of 35 cases of this not unusual syndrome. Roentgenograms and sections revealed changes similar to those seen in osteochondritides. Clinically, pain under the joint of the big toe of varied duration and intensity was the outstanding complaint. Only seldom was the onset acute. In only 3 cases was sudden trauma an apparently definite factor. On examination, local tenderness and pain on hyperextension of the toe were marked. Occasionally swelling existed. Static deformities of the feet were often found. The roentgen findings were most significant: disintegration, changes in form, vacuolation, sequestrum formation and loss of normal trabecular structure might be seen. Frequently portions of a sesamoid up to one-third its volume were seen as free bodies. Conservative pad support and physical therapy gave relief in most of these cases. Roentgen findings in one case did not appreciably change in one and one-half years. To demonstrate the sesamoid changes best, the authors placed the patient in a prone position. The big toe was strongly dorsiflexed, placed on the film, and the x-rays were projected from the dorsal aspect. The interpretation of the pathologic process in terms of causation was difficult, but there was evidence suggesting the effect of gradual, repeated traumas as the probable cause. In one specimen, arthritis of the joint was present as well. Removal of the affected sesamoid was easily accomplished. When conservative therapy was not successful, removal of the sesamoid through a plantar incision was indicated and led to rapid cure. No ill effects were noted in consequence of its excision.

[ED. NOTE.—Pain referable to the sesamoid is rare, and excision of the sesamoid is rarely justifiable in the experience of the editors.]

*Study of the Blood Supply of the Ligamentum Teres and Its Relation to Circulation of the Head of the Femur.*—Chandler and Kreuschnner<sup>37</sup> studied 114 round ligaments from 68 cadavers, the average age of which was 48 years. In all but one of the ligaments they found blood vessels which branched in the femoral head. In any surgical operation on the hip, preservation of the intact round ligament was considered most important.

*Circulation of the Head and Neck of the Femur.*—Forty-one cases of intracapsular fracture of the neck of the femur were studied by

36. Kimmelstiel, P.; Kremger, K., and Richter, H.: Arch. f. klin. Chir. **172**: 403, 1932.

37. Chandler, S. B., and Kreuschnner, P. H.: J. Bone & Joint Surg. **14**:834, 1932.

Wolcott.<sup>38</sup> The cases with nonunion showed increased density of the head by roentgen examination. In addition early (time intervals were not given) absorption of the femoral neck was noted. This continued until the entire neck had disappeared. Four patients were operated on, and the ligamentum teres removed for examination. In all cases microscopic sections showed patent blood vessels in the ligamentum teres. The ages of the patients were 60, 72, 76 and 63. Blood supply through the ligamentum teres was therefore considered to be a definite factor in maintaining the nourishment of the femoral head. Consequently, operations on the hip joint should be designed and carried out in such a way as not to disturb or injure the vessels coming through the ligamentum teres. The author was careful to state that the femoral head had other sources of nourishment and that other factors besides circulation entered into the production of nonunion.

*Production of Increased Compression Strength of Bone.*—Using a special machine which measured the compression strength of bone, Ross<sup>39</sup> showed that the operations carried out by Barth and Archibald to increase the strength of bone in cases of juvenile osteomalacia and fragilitas ossium were not effective. The operations consisted of removing subperiosteally longitudinal segments from the long bones, grinding or rongeurizing these and placing them in the marrow cavity. Ross showed, however, that if detached strips of muscle were placed in the marrow cavity, deep to the fragmented bone, that the strength of the healed bone was enormously increased, in 1 case over 100 per cent. Histologically, the muscle was found to have been replaced by bone, with a consequent final thickening of the cortex. At least four months were required for the development of the extra strength.

*Calcareous Deposits in the Supraspinatus Tendon.*—Seven cases in which operation was done for calcareous deposits in the supraspinatus tendon were described by Emslie.<sup>40</sup> In three of these, small cavities were found in the head of the humerus. Examination of 162 mg. of the ash of one of the deposits demonstrated the composition to be 116 mg. of calcium phosphate, 15 mg. of calcium carbonate and 31 mg. of undefined ash. All cultures taken at operation were sterile. The most characteristic finding was tenderness over the tip of the shoulder. Total extirpation, with curetting of the cavity, if present, was advocated, even if this entailed the opening of the shoulder joint. The approach was by retracting the anterior border of the deltoid muscle.

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38. Wolcott, W. E.: *Circulation of the Head and Neck of the Femur: Its Relation to Nonunion in Fractures of the Femoral Neck*, J. A. M. A. **100**:27 (Jan. 7) 1933.

39. Ross, D.: *Brit. J. Surg.* **20**:337, 1932.

40. Emslie, R. C.: *Brit. J. Surg.* **20**:190, 1932.

*Antigrowth Principle Derived from Parathyroid Extract.*—By injecting an extract of parathyroid gland from which the blood calcium-raising principle has been removed into various experimental animals, Robinson and Thompson<sup>41</sup> showed that a great retardation of growth was brought about. The retardation was approximately equivalent to the quantity of extract given. In some cases tolerance was developed. The antigrowth principle was not isolated, but some information was obtained relating to its properties.

#### FRACTURES

*Colles' Fracture.*—Three years of experience in treating Colles' fractures with plaster-of-paris fixation for five weeks, as advocated by Böhler, convinced Platt<sup>42</sup> that nothing was lost in either the function or the nutrition of the part by the elimination of physical therapy, and that the risks of recurrent deformity were minimized.

[ED. NOTE.—This is an interesting point of view. The editors believe that physical therapy still has a place in the treatment of Colles' fracture.]

*Treatment of Fractures in the Light of Their Ischemic Complications.*—Girdlestone<sup>43</sup> discussed ischemic complications of fractures and divided them as follows: (1) Volkmann's ischemic contracture, the result of sudden localized pressure; (2) an ischemia due to relatively prolonged and widespread contraction and disuse, occurring characteristically in older patients and due to a localized sympathetic dysfunction, and characterized by swelling, coolness and stiffness of the part; (3) ischemia at the site of a fracture, as in the case of the carpal scaphoid, the femoral neck and sometimes the long bone, designated by the author as traumatic arterial ischemia. The treatment of each was discussed, i. e.: (1) early recognition of a Volkmann's contracture, and fascial decompression if necessary; (2) avoidance of too prolonged fixation, and (3) accurate reduction and efficient fixation followed by proper forms of physical therapy to improve circulation to the part, and improvement of the local sympathetic response.

#### RESEARCH

*Studies on Tendon Repair.*—Mason and Shearon,<sup>44</sup> in an exhaustive experimental study of tendon repair in dogs, found that within one

41. Robinson, M. H. B., and Thompson, J. H.: J. Physiol. **76**:303, 1932.

42. Platt, H.: Brit. M. J. **2**:288, 1932.

43. Girdlestone, G. R.: J. Bone & Joint Surg. **14**:755, 1932.

44. Mason, M. L., and Shearon, C. G.: Progress of Tendon Repair: Experimental Study of Tendon Suture and Tendon Graft, Arch. Surg. **25**:615 (Oct.) 1932.

week after suture of the tendon a fairly firm union was affected by proliferation of sheath tissues. This was gradually invaded and replaced by proliferation of the tendon cells themselves, a minimum of two weeks being required to establish firm union. They concluded that in suture of the tendon the sheath should be carefully closed, if possible. Accurate end-to-end approximation of the ends of the tendon was important, and defects should be bridged by free tendon grafts with their sheath tissue intact rather than by fascia, which tended to stretch. Movements might be begun on the fifth or sixth day, but no strain should be placed on the tendon before the third week.

*Repair of Articular Cartilage.*—In the joints of normal adult dogs, Bennett and Bauer<sup>45</sup> produced defects in the articular cartilage; in some they displaced the patellae so as to cause abnormal friction. They also studied the effect of disarticulation of the joint on the cartilage. The joints were studied at intervals of four, twelve, twenty-two and twenty-eight weeks. Their conclusions were: 1. Cartilage had a limited ability to repair aseptic lesions within its substance by independent regeneration of cartilage, and the repair was more perfect over the mesial femoral condyle than in the patellar groove. 2. Portions of cartilage excised from the joint and later returned to the joint cavity were usually walled off by fibrous tissue and removed from the joint space. 3. In the cases in which defects extended into subchondral bone, and in the joints in which the patellae had been displaced, the reparative changes passed through stages of fibrous tissue and fibrocartilage to the formation of an imperfect hyaline cartilage. In disarticulated joints, extensive atrophy with pannus formation over the joint cartilage developed, demonstrating the importance of proper apposition and weight-bearing of adjoining articular surfaces.

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45. Bennett, G. A., and Bauer, W.: *Am. J. Path.* 8:499, 1932.

## RADIOSENSITIVITY OF TUMORS

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The advent of radiation as a therapeutic agent in neoplastic diseases has stimulated an enormous amount of interest in the fundamental nature of the action of radiation on tissues in general and on tumors in particular. The actual intimate mechanism by which radiation produces injury to cells is vague, and its elucidation must await prolonged biophysical analysis. On the other hand, much information is available regarding the various types of cells or tissues which are especially susceptible to injury by radiation, together with certain of the conditions under which they exhibit this susceptibility. The histologic changes following irradiation have been abundantly described. Much of this knowledge has come from the study of the behavior of tumors under radiation, and from these observations on the behavior of tumors have been formulated certain generalizations which have been called laws of radiosensitivity. It must be realized that these laws are expressions of observed facts and not ultimate explanations of facts, and yet from a pragmatic point of view they constitute an increasingly valuable body of data for the clinician or pathologist interested in cancer.

In the earlier days of therapeutic radiology it became apparent that the distinctly embryonal tumors were highly sensitive to radiation. On the morphologic side such tumors are composed of particularly delicate cells. The cytoplasm is delicate and rich in fluid content. Such cells lack a tough cell membrane. It is possible that they have a high metabolic rate, although little is known about comparative tumor metabolism. Prominent among such embryonal tumors are the embryomas of the testis and ovary, and the Wilms tumors of the nephrogenic anlagen. With the differentiation of such tumors into the adult teratomas or the relatively adult renal tissues the radiosensitivity diminishes. The embryonal adenocarcinomas of the testis are distinctly more resistant, and fully developed adult teratoma is a resistant tumor. Is the difference dependent on changes in the metabolic rate? Possibly, although, judging by the rate of growth, the metabolism of embryonal adenocarcinoma of the testis is certainly high. The susceptibility of embryonic

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This paper was prepared at the request of the American Society for the Control of Cancer as one of a series of monographs on subjects of interest and importance to those engaged in the diagnosis and treatment of cancer.

tissues to various noxious agents in correlation with the particular metabolism of the injured region is well known (Stockard<sup>1</sup> and others). Small differences in the developmental age of biologic test objects may make enormous differences in the amount of radiation necessary to prevent further development. Henshaw and Henshaw<sup>2</sup> have shown, for example, that if it requires from 300 to 400 roentgens to produce a 50 per cent mortality in recently deposited *Drosophila* eggs during the cleavage and blastula stage, the necessary quantity rapidly increases to from 1,200 to 2,000 roentgens during the stage of gastrulation. Packard<sup>3</sup> has shown that if cell activity is depressed by lowering the optimum developmental temperature and hence the metabolic rate, the quantity of radiation necessary to kill is increased. Exposed at 23 C. it required a treatment of ten and one-half minutes to kill 50 per cent of *Drosophila* eggs. At 13 C. it required thirteen and two-tenths minutes, and at 28 C., but nine minutes. Strangeways and Fell<sup>4</sup> irradiated chick embryos and following the irradiation kept some in the incubator and others at 0 C. for five hours. They then made cultures from both and found that the cultures from the chilled embryos grew well, but that those from the incubated cultures grew little or not at all. They are of the opinion that sensitivity is lowered in the cold because the metabolic rate is lowered. Studies of this sort are of enormous general significance, and yet so little is known concerning the special metabolism of tumors that for the present they cannot be directly applied to explain the sensitivities of specific tumors.

A high metabolic rate may be assumed for rapidly growing anaplastic tumors, but unfortunately not all such tumors are sensitive to radiation and some are highly resistant. Nor is one greatly assisted in the search for the explanation of the sensitivity of such tumors by their large number of mitoses. It seems certain that cells exhibit a heightened sensitivity sometime during the mitotic or premitotic period (Regaud,<sup>5</sup> Strangeways and Hopwood<sup>6</sup> and Seide<sup>7</sup>), but in a tumor the number of mitoses varies from region to region and from section to section. Furthermore, no one knows the frequency and duration of the mitotic cycle, and observations have shown that tumors full of mitotic divisions may be either sensitive or resistant, depending on their fundamental nature.

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1. Stockard, C. R.: *Am. J. Anat.* **28**:115, 1921.
  2. Henshaw, P. S., and Henshaw, C. P.: *Radiology* **21**:239 (Sept.) 1933.
  3. Packard, Charles: *J. Cancer Research* **14**:359, 1930.
  4. Strangeways, T. S. P., and Fell, H. B.: *Proc. Roy. Soc., London, s.B.* **102**:9, 1927.
  5. Regaud, C.: *Bull. Assoc. franç. p. l'étude du cancer* **12**:482, 1923.
  6. Strangeways, T. S. P., and Hopwood, F. L.: *Proc. Roy. Soc., London, s.B.* **100**:283, 1926.
  7. Seide, J.: *Deutsche med. Wchnschr.* **54**:523, 1928.

Certain tumors seem to exhibit inherent qualities of radioresistance, possibly related to marked resistance in the tissue of origin as, for example, in the neurosarcoma, glioma and melanoma groups. Assuming with the Masson school the nervous origin of neurosarcoma (schwannoma) and melanoma, it is easy to believe that these tumors are resistant because they develop from a resistant soil, yet this explanation remains a hypothesis only. Ewing<sup>8</sup> stated that "throughout the entire list of malignant and benign tumors one can trace the influence of the intrinsic properties of the cells of origin." In fact, in the case of many individual tumors the fundamental nature of the tissue of origin outweighs all other considerations when an attempt is made to estimate the sensitivity.

One of the most important factors which is associated with resistance of tumors is the property or tendency of the tumor cells to excite desmoplastic reactions in the host. The question as to whether desmoplasia causes a reduced sensitivity, or whether tumor cells which show some slowing down of their growth activity and hence probably of their metabolic rate permit the development of host tissue reactions—the radioresistance and the desmoplasia thus being two expressions of a single phenomenon—cannot be decided. Nevertheless, the practical significance of reduced radiosensitivity in the presence of fibrosis is unaltered. This question of fibrosis will be referred to later in the discussion of the actual histologic changes produced in tumors by radiation.

On the basis of histologic studies it is frequently noted that when portions of a tumor regress and other portions fail to vanish, the latter regions may be characterized by the presence of productive fibrosis. In many sensitive tumors, however, if studies are made during the period of rapid regression, isolated cells or cell islets may be found which fail to show necrosis (fig. 1). I have not been able to relate these living islands to local vascular conditions or to the state of the connective tissue with great uniformity and feel more inclined to associate them with inherent differences in the individual cell population. Packard<sup>9</sup> has plotted from Wood's data<sup>10</sup> the mortality curves, showing the relation between the percentage of takes at transplantation of different animal tumors and dosage prior to transplantation. The curves show a fairly wide variation which may or may not be of the symmetrical type. Thus the threshold dose for the Flexner rat carcinoma is 200 roentgens, and the full lethal dose, 2,200 roentgens. Twelve hundred roentgens kills 50 per cent of the tumors. In another instance (tumor 8), one-half the cells are killed by 300 roentgens, but 1,500 roentgens

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8. Ewing, James: *Radiology* **13**:313, 1929.

9. Packard, Charles: *J. Cancer Research* **11**:282, 1927.

10. Wood, F. C.: *Radiology* **5**:199, 1925.



is needed to destroy all of them. The work indicates rather marked differences in the susceptibility of cells which to other intents and purposes seem quite uniform. The wide differences between the dose causing tumor regression and that necessary for the cure of disease are only too apparent in the field of cancer in human beings.

It has long been known that severe anemia or cachexia is prejudicial to a normal response to radiation. Such observations form the basis for the belief that active circulation in the tumor is desirable for radio-

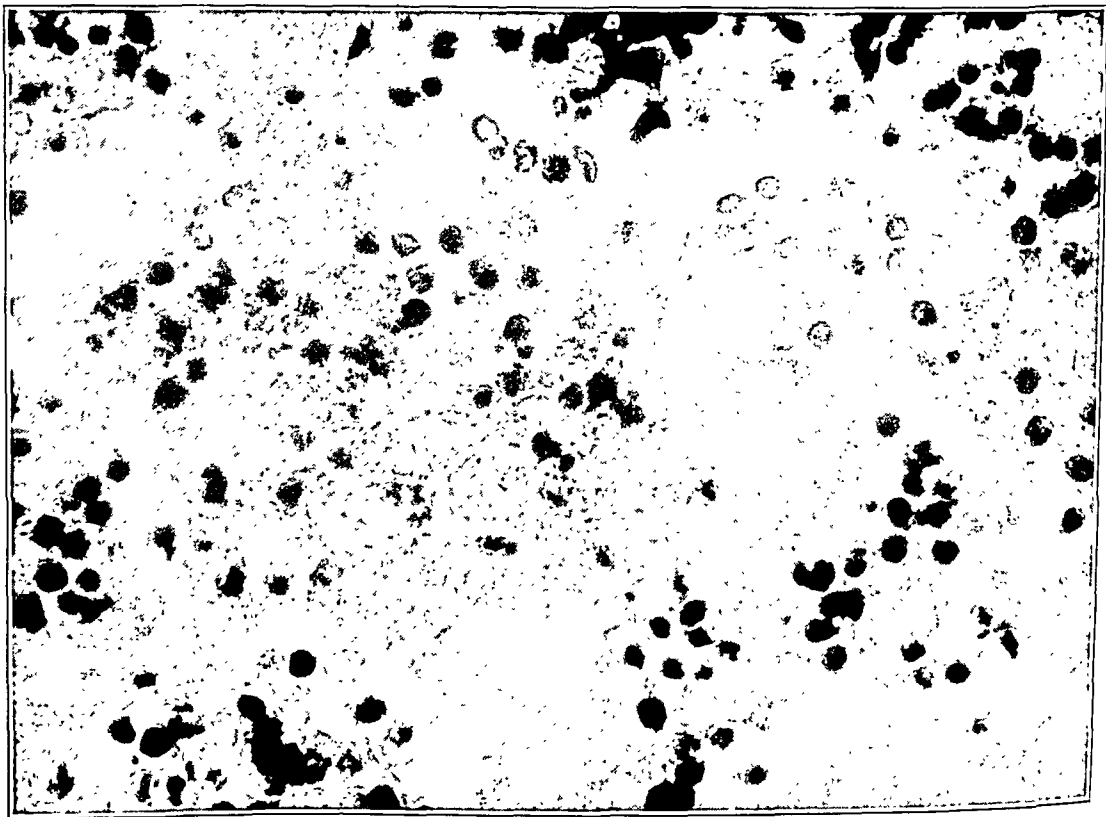


Fig. 1.—Lymphosarcoma, radiosensitive. Pyknosis and rapid cellular disintegration following treatment. The distribution of necrotic cells is quite irregular.

sensitivity, that the body reacts to radiation as a whole organism and that a constitutional element plays a definite rôle in a favorable response.

Students of radiation have long held divergent views as to the mechanism by which radiation causes regression of tumors. Whereas few would deny the importance of the direct action of radiation on the tumor cell, opinions differ widely as to the importance of local changes produced in the tumor bed and also of general bodily changes. As regards the latter, I must admit that, after a review of a large literature on the subject, no safe conclusion may be reached either as to the

importance or even as to the very nature of these general bodily alterations. For a discussion of these matters the reader is referred to the critical review by Kuhlmann.<sup>11</sup>

Certain investigators are inclined to minimize the importance of a direct action of radiation on the tumor cells. This attitude has been recently emphasized by Pullinger.<sup>12</sup> She summarized the effect of radiation somewhat as follows: The early changes consist of hyperemia and injury to the endothelium of thin-walled, ill supported vessels. This injury results in edema, desquamation of cells at the surface, thrombosis, infarction, necrobiosis, exudation of serum, coagulation, extravasation of blood and trauma. She boldly concluded that all effects following irradiation are related to vascular "stimulation" and vascular degeneration. Granting that these factors are undoubtedly of significance, I cannot see quite how they can be indiscriminately applied to all tumors if one is to explain the extremely variable responses to radiation. For example, Nemenow<sup>13</sup> saw a lymphosarcoma the size of a man's head vanish within eighteen hours after rather little radiation. At the Memorial Hospital my associates and I have witnessed relief of dyspnea in certain mediastinal neoplasms follow the quantity of radiation used in fluoroscopy. Furthermore, tumors without thin-walled, ill supported vessels may be quite radiosensitive. At the Conference on Cancer held in London in 1928, Wood<sup>14</sup> and Lacassagne<sup>15</sup> drew quite opposite conclusions on the importance of vascular lesions in tumor regression. Most pathologists find explanations for the observed histologic changes following irradiation by assuming effects both on the tumor cells and on the tissue bed, the relative importance varying with the tumor. Whereas there is essential agreement on the character of these histologic changes, different students place different emphasis on their relative importance. For elaborate descriptions of the tissue changes following irradiation the reader should consult the papers of Regaud and Lacassagne<sup>16</sup> and Ewing.<sup>17</sup> For a discussion of the probable physicochemical basis of irradiation the paper of Fernau<sup>18</sup> is of interest. The latter emphasizes injuries to vessel walls and cell membranes, increased permeability of vessel and cell walls, alterations in

11. Kuhlmann, B.: *Strahlentherapie* **19**:817, 1925.

12. Pullinger, B. D.: *J. Path. & Bact.* **35**:527, 1932.

13. Nemenow, M.: *Strahlentherapie* **44**:655, 1932.

14. Wood, F. C.: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 455.

15. Lacassagne, A.: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 457.

16. Regaud, C., and Lacassagne, A.: *Radiophys. et radiothérapie* **1**:1, 1930.

17. Ewing, James: *Am. J. Roentgenol.* **15**:93, 1926.

18. Fernau, A.: *Strahlentherapie* **19**:142, 1925.

hydrogen ion concentration and osmotic pressure, changes in the rate and character of diffusion between blood and tissues, variations in surface tension, viscosity and changes of tissue colloids, flocculation of albumin-lipoid complexes, oxidative disturbances and disturbances in other chemical processes. After considerable discussion Fernau was forced to the conclusion that "aus all diesen Ausführungen ersieht man, dass wir trotz aller Bemühungen über den Mechanismus der Strahlenwirkung, keine sichere Kenntniss haben" (from all these explanations it can be seen that, in spite of all efforts, we have as yet no certain knowledge about the mechanism of ray action).

Ewing stated that underlying all tissue reactions to radiation are the primary effects on the tissue cells. He believes that both nucleus and cytoplasm suffer together in varying degree, thus differing from Regaud and Lacassagne, who are inclined to believe that the nucleus is the special point of injury. It appears to me that some justification of the views of the French school in this respect is to be found in the numerous studies of biologists working with microdissection apparatuses, which have repeatedly revealed the comparative resistance of cytoplasm to various noxious agents and the extreme susceptibility of the nucleus.

Ewing accepts as fully attested the law of Bergonié and Tribondeau,<sup>19</sup> that dividing cells are more susceptible than resting cells, and the observations of Schwarz<sup>20</sup> that susceptibility to radiation is in direct proportion to the growth metabolism of the tumor cells. I have already drawn attention to the fact that not all rapidly growing tumors are radiosensitive, although one might infer from their capacity of growth that they possessed a high metabolic rate. Ewing stated that in tumors irradiation is followed by enormous swelling and hyperchromatism of epithelial nuclei, the result of imbibition of fluid by the nuclei at the expense of the cytoplasm. The probable explanation consists in intracellular changes produced by changes in electrolytes and decomposition of salts, fats and proteins, so that water is drawn in by simple osmosis. Regaud and Lacassagne are of the opinion that the nuclear chromatin is particularly affected. Ewing finds that under other conditions and generally in the case of lymphoid and embryonal tumors, there occur pyknosis, shrinkage and karyorrhexis, which seem to occur especially when the cytoplasm is hydropic. When these changes are present in pronounced form they lead to death of the cells.

After full irradiation mitoses partially or wholly disappear. If they reappear they are apt to be abnormal in form or abortive. Schreus<sup>21</sup> found that amitotic division may replace mitotic division. That cells

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19. Bergonié, J., and Tribondeau, L.: *Compt. rend. Acad. d. sc.* **143**:983, 1906.

20. Schwarz, Gottwald: *Wien. klin. Wchnschr.* **36**:906, 1923.

21. Schreus, H. T.: *Deutsche med. Wchnschr.* **51**:358, 1925.

may recover from such damage is evidenced by frequent recurrences in scarred fibrotic beds. Under such conditions the cells are extremely resistant to further radiation.

Among the changes which seem most significant are those of the blood vessels. Ewing believes that practical irradiation often acts largely through vascular disturbances. Irradiation is followed first by hyperemia. Vasodilatation is followed by exudation, hemorrhage, rupture of the capillaries and thrombosis. The endothelial cells are swollen and hydropic. All of the vessel coats become swollen and thickened, and a late arteriosclerosis leading to an anemic cicatrix may result.

Repair in an irradiated field occurs by much the same mechanism that one finds after other injuries, but with certain peculiarities which will not be discussed since they bear especially on the phenomena of late radionecrosis, a topic quite foreign to the present paper. One of the earliest features of repair is the lymphocytic exudate. Lymphocytes gather in the irradiated field probably as the result of lymph stasis. So little is actually known about the lymphocyte, both as to its origin and as to its place as a biologic entity, that its influence on the healing process, if indeed it has any, is obscure. Ewing stated that complete destruction of tumor cell foci may follow the accumulation of lymphocytes. He accepts the contention of Murphy<sup>22</sup> that radiation acts partially through the mobilization of lymphocytes. This view is denied by Prime.<sup>23</sup> The tendency of lymphocytes to gather about foci of regressing tissue is well known. Not only do they tend to accumulate about tissue in the process of immediate regression, but throughout the biologic field they seem in their location to be particularly associated with regions where embryonal absorptive processes are under way (absorption of pharyngeal pouches, in the formation of the eustachian tube, the bursa of Fabricius, the intestinal glands, the pharyngeal tonsils and the postbranchial body—Kingsbury<sup>24</sup>). Ewing believes that the plasma cell or conditions under which the plasma cell occurs are antagonistic to the process of cancer.

Connective tissue proliferation occurs in the healing process under many circumstances. Cellular connective tissue with considerable momentum of growth may develop in irradiated lymph nodes, in muscles and in the subcutaneous tissue. The active proliferation of connective tissue may usually be traced to marked injuries to the normal tissue during the irradiation. In some nodes Ewing followed the

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22. Murphy, J. B.: *The Lymphocyte in Resistance to Tissue Grafting. Malignant Disease and Tuberculous Infection*, New York, Rockefeller Institute for Medical Research, 1926, monograph 21.

23. Prime, Frederick: *J. Cancer Research* 6:1, 1921.

24. Kingsbury, B. F.: *Am. J. Anat.* 50:201, 1932; 51:269, 1932.

process into almost a sarcoma-like growth. Thus Weigert's law may be abundantly fulfilled. New capillary growth may be extreme. In one instance Ewing traced the development of a recurring angiosarcoma in a roentgen ulcer.

With the marked destruction of tissue cells a form of indolent connective tissue essentially devoid of circulation may result. To this type of tissue the term abortive fibrosis has been applied. It occurs especially after repeated irradiation and is one of the end-products of unsuccessful irradiation, since tumor cells may long remain in areas of abortive fibrosis. Such cells are extremely resistant. They have acquired a resistance greater than that of the surrounding connective tissues. The reaction of fat tissue to radiation is peculiar. Fat breaks down into oil cysts, saponification appears, and considerable proliferation of fat cells ensues. The response of the connective tissue is poorly developed, and fat tissue constitutes an unfavorable bed for the irradiation of tumors. The peculiar reaction of fat tissue to radiation has a definite bearing on certain problems of practical irradiation, particularly the irradiation of mammary cancer in the fatty breast.

Regaud<sup>25</sup> recognized in many neoplasms, especially in epidermoid carcinomas, a source of the neoplastic cells (*souche cellulaire*) and a collateral development (*lignes laterales*). He believes that the collateral line—in epidermoid carcinoma the hornified squamous layers—has nothing to do with the perpetuation of the neoplastic process, since these cells are destined to differentiation and ultimate destruction. He sees in irradiation, when effective, an effect mainly on the *souche cellulaire*. This *souche cellulaire* in different tumors shows different radiosensitivities. Regaud believes that, for instance, in the cervix, those tumors are more radiosensitive where the *souche cellulaire* comprises a small portion of the growth and where there is a pronounced tendency for the development of collateral lines of adult squamous character. The experience at the Memorial Hospital has been somewhat different. Ewing believes that the capacity for growth of differentiating squamous cells in squamous carcinoma is long retained and that they may at a late period become mother cells. I favor the latter opinion. Late recurrences in many squamous carcinomas, when repeated biopsies have shown only atrophic-looking, hyaline squamous pearls, seem to reveal even the differentiated cell of squamous carcinoma in a sinister light.

Regaud looks on glandular carcinomas with evidences of secretion as radioresistant, since they represent differentiated adult characters. I am fully in agreement with this contention. Furthermore, overproduction of secretion, mucin, etc., appears antagonistic to irradiation fibrosis.

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25. Regaud, C.: *Radiophys. et radiothérapie* 1:443, 1930.

Regaud states that prior treatment with radiation followed by regeneration of the tumor is succeeded by radioresistance. Microbic invasion with evidences of inflammation diminishes radiosensitivity. This is likewise the view at the Memorial Hospital. Inflammation appears to interfere with the normal response of the tissue bed.

All experienced workers in the field of radiation emphasize the importance of the integrity of the tumor bed. The integrity of the circulation for a normal response to radiation has been shown experimentally by Jolly.<sup>26</sup> He proved that vasoligation prior to irradiation diminished the effect of radiation. Mottram<sup>27</sup> stated that if experimental tumors are irradiated and left for four or five days in the animal and then transplanted, they are less apt to grow than when they are irradiated and transplanted immediately. He believes that the difference is due to the effect of radiation on the blood supply. The effect of ischemia in diminishing sensitivity has been shown by Ferroux, Jolly and Lacassagne<sup>28</sup> and by Ferroux and Regaud.<sup>29</sup> One must distinguish between initial ischemia and ischemia developed as a result of irradiation. In resistant tumors, when an effort is being made to reduce the rate of tumor growth, an induced ischemia appears highly desirable. It is well known that massive destruction of a tissue bed by radiation is dangerous. With irradiation paralysis of fibroblastic activity, residual tumor cells may proliferate with great rapidity. A quotation from Lacassagne<sup>30</sup> may be appropriate. He stated:

Si le but à atteindre en radiothérapie des cancers doit être avant tout de détruire les cellules néoplastiques, il ne faut pas méconnaître cependant l'importance qu'il y a à ménager les tissus généraux. En réalisant ces deux objectifs, on obéit à une ligne de conduite depuis longtemps formulée, et qui semble la meilleure condition de succès: administrer, à toutes les cellules cancéreuses, la plus forte dose compatible avec l'intégrité des tissus sains. (If the goal to be attained in radiotherapy of cancers is, above all, the destruction of the neoplastic cells, one must not disregard the importance of exercising caution with regard to the general tissues. In realizing these two objectives, one follows a line of conduct formulated long ago which seems to be essential to success: administer to all the cancerous cells the strongest dose compatible with the integrity of the healthy tissues.)

The question may be asked as to what type of tumor response indicates radiosensitivity. Lymphosarcomas are radiosensitive. They disappear dramatically. On the other hand, there are certain neurogenic sarcomas which vanish under irradiation. These are rare. Their disappearance is slow and progressive and may require a year for com-

26. Jolly, J.: *Compt. rend. Soc. de biol.* **91**:532, 1924.

27. Mottram, J. C.: *Brit. M. J.* **1**:275, 1927.

28. Ferroux, R.; Jolly, J., and Lacassagne, A.: *Compt. rend. Soc. de biol.* **95**:646, 1926.

29. Ferroux, R., and Regaud, C.: *Compt. rend. Soc. de biol.* **97**:663, 1927.

30. Lacassagne, A.: *Radiophys. et radiothérapie* **1**:401, 1930.

pletion. Obviously, these tumors are not sensitive in the ordinary sense. The process is one of slow sclerosis. Such examples might be multiplied many times. Then, again, there is the response of uterine myomas to radiation. Here it is extremely likely that the process has essentially nothing to do with the influence of radiation on the myoma, and that the chief effect is on the ovary. This is not radiosensitivity. I should define radiosensitivity as that combination of circumstances resident in the tumor or the host which permits marked or total local tumor regression under doses of radiation sufficiently small to preserve the essential integrity of the host's tissue. This definition eliminates from the sensitive group those tumors which require heavy interstitial irradiation. In defining the integrity of the host tissue I mean essentially the immediate integrity and am less concerned with late vascular disturbances. The definition is admittedly unsatisfactory. Many tumors usually regarded as radiosensitive are close to the borderline. Witness, for example, the hypopharyngeal group in which after external irradiation by divided dose methods the tumor may completely regress, and yet the tissue may be so damaged, although soft and pliable to external examination, that by progressive vascular changes, especially with minor infections or injuries, an extensive late necrosis may result. This is due to the fact that although these tumors tend to regress markedly under intermediate ranges of irradiation it is known that, with doses approaching the limit of tolerance, they may be completely sterilized. Thus the doses used usually reach nearly the limit of tolerance in the effort to cure a radiosensitive tumor completely.

The term "total" local tumor regression as used in the definition is also unsatisfactory. It is meant to imply complete absence of clinically ascertainable disease in the area treated. This does not necessarily mean absence of histologic disease, since it is often a fact that apparently highly sensitive tumors reappear in an almost explosive fashion after seemingly complete anatomic regression. Thus, radiosensitivity does not necessarily mean that the tumor may be cured by irradiation. Moreover, as will be seen later, histologic disease may not mean clinical disease.

Degrees of radioresistance are likewise recognized. Tumors which require large doses of interstitial radiation are considered resistant, but radioresistance does not necessarily mean that the disease is not controllable by radium. It should be emphasized that the relative character of sensitivity and resistance must dominate the discussion.

The reader must realize that efforts to correlate tumor structure with response to radiation constitute a relatively new field of radiologic pathology. In the case of certain tumors, notably the epidermoid carcinomas, definite progress has been made, and yet considerable differences of opinion exist. Much information is available concerning the various embryonal carcinomas, the lesions of the lymphatic and myeloid

apparatus and tumors of the bone, and the extreme radioresistance of specific types of tumors, such as melanomas or neurosarcomas, is well known. With many other tumors the available information is much too scanty to enable one to draw definite conclusions. For example, little is known concerning the relation of structure to radiosensitivity in carcinomas of the corpus uteri, although these lesions have been treated by radiation in some clinics for years. Little is known of the comparative behavior of different types of cancer of the breast and ovarian carcinoma, and essentially nothing regarding tumors of the bladder, prostate and gastro-intestinal tract. There is a common tendency to confuse grade of malignancy with radiosensitivity, although these properties are in many instances quite distinct and independent, although they parallel one another occasionally. Radiosensitivity is confused with cure by irradiation. Many papers show little or no effort to correlate successes or failures with pathologic findings, and there is a tendency casually to dismiss the failures without an attempt at pathologic analysis.

It is my intention to discuss in the following pages the behavior to irradiation of the various tumor types, dealing with them largely as specific entities, with the idea that generalities, as usually expressed, afford the practical radiotherapist rather small information on what may be anticipated with the individual tumor. The effort has been to produce a practical paper rather than one dealing purely with the theoretical and analytic aspects of radiosensitivity. Of several hundred references, those have been selected in which the authors made some statement as to a correlation between structure and sensitivity even though merely to the effect that none could be detected. In the case of some tumors it has been possible to state only that a certain author observed disappearance of tumors with external irradiation alone, thus offering a proof of the existence of a limited number of radiosensitive tumors of the region concerned, without specification as to histologic types. It has been found impracticable to cover the entire radiologic literature on the subject, and hence only more significant contributions have been quoted. The radiologic literature has grown at such a rate that I offer no apology for this restriction.

In illustration, an effort has been made to picture specific groups only, rather than to produce a histologic atlas of neoplastic diseases.

#### INTRA-ORAL CARCINOMA

Much is known about the radiosensitivity of intra-oral carcinoma. Errors in properly predicting the irradiation behavior of intra-oral cancers show that much remains to be learned. Intra-oral cancer is not a single disease but a group of related entities varying in structure, irradiation behavior and clinical course. Tumors of similar structure and in similar anatomic settings may behave differently in different persons. Regaud has emphasized that the cells of origin (*souche cellu-*





Fig. 2.—Intra-oral cancer; highly resistant spindle cell epidermoid carcinoma (A) beneath epidermis and (B) invading muscle.

laire) differ in sensitivity in different portions of the same tumor and hence obviously from one tumor to another of similar structure. This does not necessarily mean that predictions of radiosensitivity are of no value. In checking over the cases of approximately 100 patients with hypopharyngeal tumors who were treated within the last two years at the Memorial Hospital, I found that the predicted radiosensitivity was erroneous in about 10 per cent. The error has usually been in the direction of an underestimated rather than an overestimated sensitivity. If one attempts to judge sensitivity from the section alone, the errors are increased. I prefer to know the gross character of the lesion, the exact location and the duration of the disease. It is important to know whether the gross lesion is decidedly papillary in structure, since papillary tumors are apt to be more sensitive. The location is important, since tumors of the same structure histologically differ somewhat in their radiosensitivities in different regions. Tumors of long duration and with pronounced infiltrative characters are apt to be desmoplastic and correspondingly resistant.

Epidermoid carcinomas of the oral cavity differ in structure. The adult squamous carcinomas tend to occur on the lip, the dorsum, tip and lateral borders of the tongue, the alveolar ridges, the hard palate, the buccal mucosa, the pharyngeal vault and the true vocal cords (figs. 3 and 4). As a group these tumors are radioresistant. In a series of patients treated by measured doses, Martin, Quimby and Pack<sup>31</sup> estimated that they require from 7 to 10 skin erythema doses<sup>32</sup> for control. This requirement places these tumors in the resistant class, since their regression appears to require interstitial irradiation in some form. It is well known that these doses approach the tolerance of the normal structures of the oral cavity. Hyaline necrosis of the lingual muscle in the vicinity of the lesion always results. If the tumors are near bone, i. e., on the alveolar ridge, this dose may result in osteomyelitis or productive and rarefying osteitis, especially when the lesion is accompanied by pronounced dental and oral sepsis. If the lesion invades bone it is extremely radioresistant. Irradiation, with this dose, of lesions of the pharyngeal vault results in vertebral osteitis or periosteitis, with fibrosis of the prevertebral fascias, which leads to prolonged pain. Vascular lesions and hemorrhages are common, especially with lesions situated toward the base of the tongue and hypopharynx. In debilitated persons the epithelitis may result in aspiration pneumonia or abscesses of the lungs. The radiosensitivity of the adult squamous carcinomas varies. Occasionally, a papillary lesion of pronounced adult structure is quite

31. Martin, H. E., and Quimby, E. H.: *Am. J. Roentgenol.* **23**:173, 1930.  
Martin, H. E.; Quimby, E. H., and Pack, G. T.: *ibid.* **25**:490, 1931.

32. I appreciate the desirability of expressing doses in roentgens. So far, radon doses cannot be so expressed.

sensitive. Pronounced infiltrative properties resulting in desmoplastic features usually mean higher resistance. There exists a group, fortunately small, of spindle cell epidermoid carcinomas made up of large spindle cells, producing a pseudosarcomatous appearance (fig. 2). These lesions are extremely resistant. They recur after doses sufficient to destroy much normal tissue. After unsuccessful irradiation of the

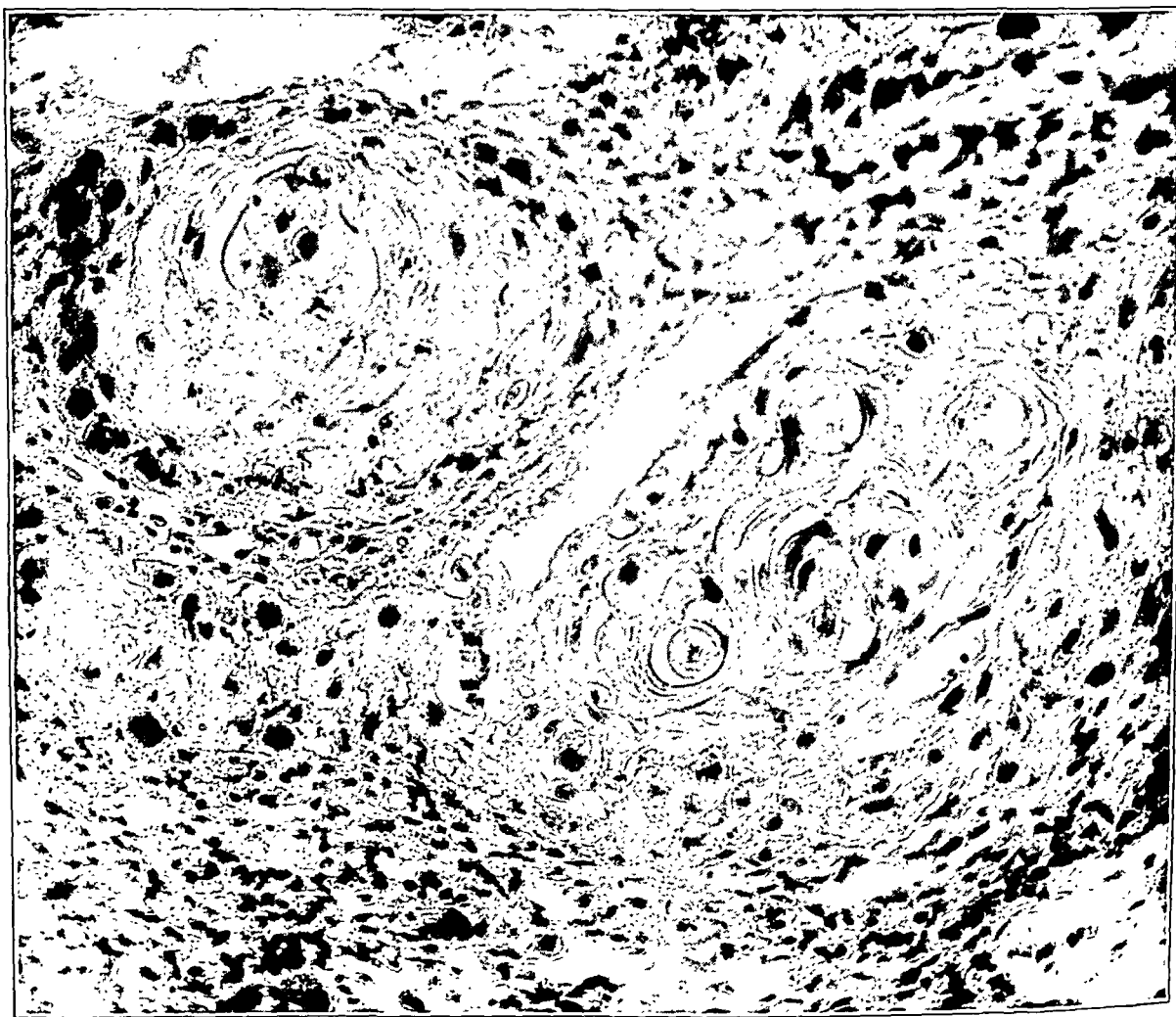


Fig. 3.—Intra-oral cancer; differentiated radioresistant squamous carcinoma.

usual squamous carcinoma of the oral cavity, the recurrence may exhibit marked desmoplastic characteristics, or else the tumor may show a spindle cell metaplasia. When metaplasia is present, the tumor is extremely resistant. It is believed that any prior unsuccessful irradiation increases the radioresistance of the tumor and the sensitivity of the surrounding tissues. It is well to recall Regaud's statement: "le traitement antérieur à forte dose par les radiations, suivi de repullula-

tion, crée peu à peu un état de radioimmunisation absolue" (previous treatment, by irradiation with high doses, creates, little by little, a state of absolute radioimmunization). Tumor cells surrounding radium ulcers with infection are resistant.

Carcinomas of the anterior floor of the mouth are apt to be papillary. They are rather soft, fungating, pinkish, vascular growths which may excavate early. They are often of the mucous membrane type—that is, with a slight tendency to pearl formation—and moderately ana-



Fig. 4.—Intra-oral cancer; relatively differentiated radioresistant squamous carcinoma.

plastic. These tumors tend to be relatively radiosensitive, though not highly so. Marked regressions may be expected under large doses of external radiation, but supplemental interstitial irradiation is usually necessary for complete local control. The mucosa of that region is rather more sensitive than that of the tongue. Furthermore, the region is a dependent one. This fact, coupled with the tendency toward early excavation, tends to lead to unpleasant radium ulcers after interstitial irradiation. Sepsis then spreads occasionally through the fascias of the floor of the mouth as far as the larynx, and death results from laryngeal edema.

Most carcinomas of the lip are radioresistant. They are sufficiently so to require either radiation from three surfaces by radium or radon applied in plastic molds, or buried radium, in order to secure regression. With these methods Regaud and his colleagues<sup>33</sup> reported 86 per cent local cures. Squamous carcinomas of the buccal mucosa tend to be radioresistant.

Carcinomas of the hypopharyngeal region, tonsil, base of the tongue and soft palate tend to be from moderately to highly radiosensitive. There seems to be a fairly close correlation between histologic structure and radiosensitivity. This is shown by the studies of Coutard,<sup>34</sup> and is amply confirmed by the experiences at the Memorial Hospital, those of Berven<sup>35</sup> dealing mainly with tonsillar tumors, and the studies of others. Coutard divided his tumors into six types: (1) nonepidermoid epitheliomas, (2) lympho-epitheliomas, (3) epidermoid epitheliomas of the mucosal type, with little differentiation and with basal cells predominating, (4) well differentiated epitheliomas of the mucous membrane, with varying degrees of stratification, (5) epitheliomas approaching the structure of cutaneous types and (6) special varieties, notably the glandular epitheliomas. The nonepidermoid epithelioma consists of cells of equal size, decidedly embryonal in character, with nuclei of uniform size and containing a fine chromatin network. I am uncertain just how this type fits with our own classification at Memorial Hospital. Coutard secured his best results in classes 1, 2 and 3. He reported but 1 cure in 13 cases of type 4; 1 in 8 cases of type 5, and 1 in 5 cases of type 6. At the Memorial Hospital we employ a simpler classification, namely, squamous carcinoma with varying degrees of adult character as judged by cornification, transitional cell carcinoma (fig. 5), lympho-epithelioma (Regaud and Schmincke types) and adenocarcinoma. We find lympho-epithelioma (figs. 6 and 7) highly sensitive as a rule; transitional cell carcinoma, from moderately to highly sensitive; the undifferentiated squamous carcinomas, moderately sensitive; the differentiated squamous carcinomas, relatively resistant, rarely from moderately to highly sensitive, and the glandular types, radioresistant. Even spindle cell cancers may be sensitive when they occur posterior to the anterior palatoglossal fold. Berven insisted on the importance of histologic determinations of radiosensitivity, and Coutard expressed the belief that the histologic structure of tumors of the pharynx and larynx outweighs in importance, for therapeutic purposes and prognosis, even the extent of involvement of the cervical nodes.

33. Regaud, C.; Lacassagne, A.; Roux-Berger, J. L.; Coutard, H.; Monod, O.; Pierquin, J., and Richard, G.: *Strahlentherapie* 26:221, 1927.

34. Coutard, H.: *Radiophys. et radiothérapie* 2:541, 1932.

35. Berven, E. G. E.: *Malignant Tumors of the Tonsil*, *Acta radiol., supp.* 11, 1931, p. 1.

Coutard noted that the time of appearance of radio-epithelitis varies in different portions of the oral cavity and indicates a varying sensitivity of these territories which corresponds in general to the sensitivities of tumors arising from these regions. Thus, the earliest region to show membrane formation is the mucosa of the tonsillar pillars and the soft palate. The vallecule, the pharyngolaryngeal folds and the floor of the mouth show inflammatory changes slightly later. The laryngeal aspect of the epiglottis, the interarytenoid space and the base of the tongue

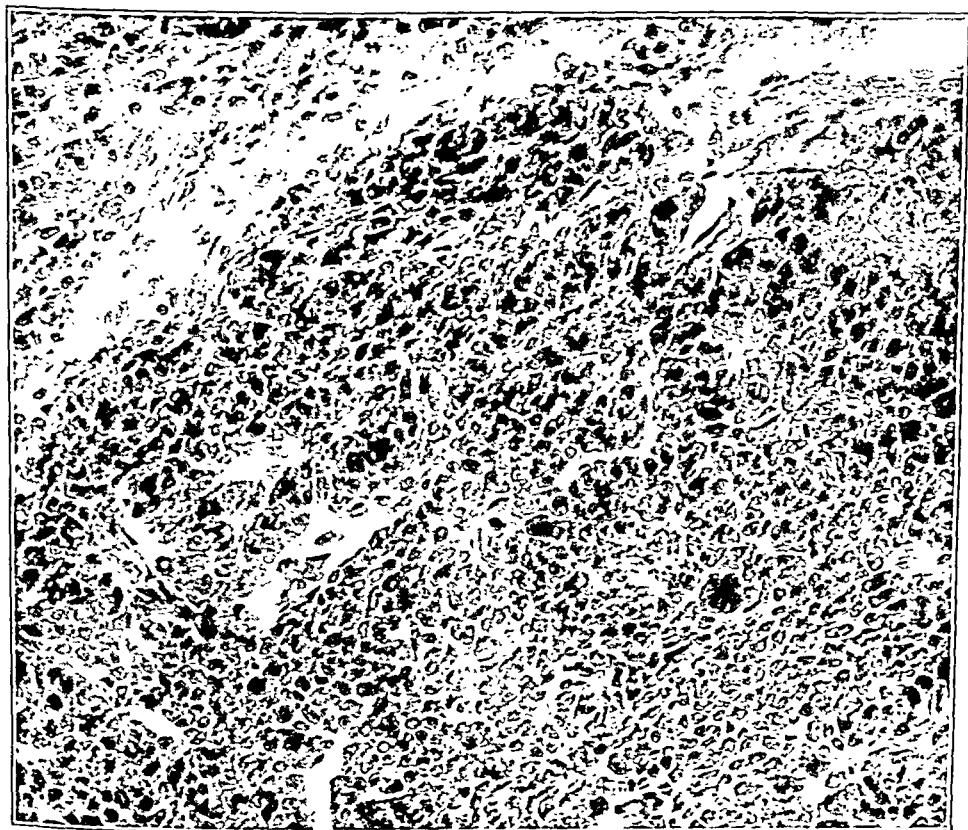


Fig. 5.—Intra-oral cancer; relatively radiosensitive transitional cell carcinoma.

require a slightly larger dose to produce epithelitis, and the inflammatory process on the vocal cords and dorsal and anterior aspects of the tongue does not appear until several days later. The time of appearance of these lesions corresponds fairly well to what is known of the sensitivity of tumors arising in the regions. According to our own ideas, the time of appearance of the epithelitis on the cheek and on the mucosa over the mandible (according to Coutard, the epithelitis appears there before it does over the base of the tongue) does not fit with the observed resistance of tumors in this location.

It has been emphasized that although these hypopharyngeal, uvular and tonsillar types are generally radiosensitive, the doses to which they respond with complete regression are often close to the limit of normal tissue tolerance. Naturally, this normal tissue tolerance varies somewhat in different persons. A dose sufficient to cause marked regression or sterilization almost invariably causes xerostomia and disturbances in the sense of taste. It may cause chronic edemas, chronic fibrosing myositis

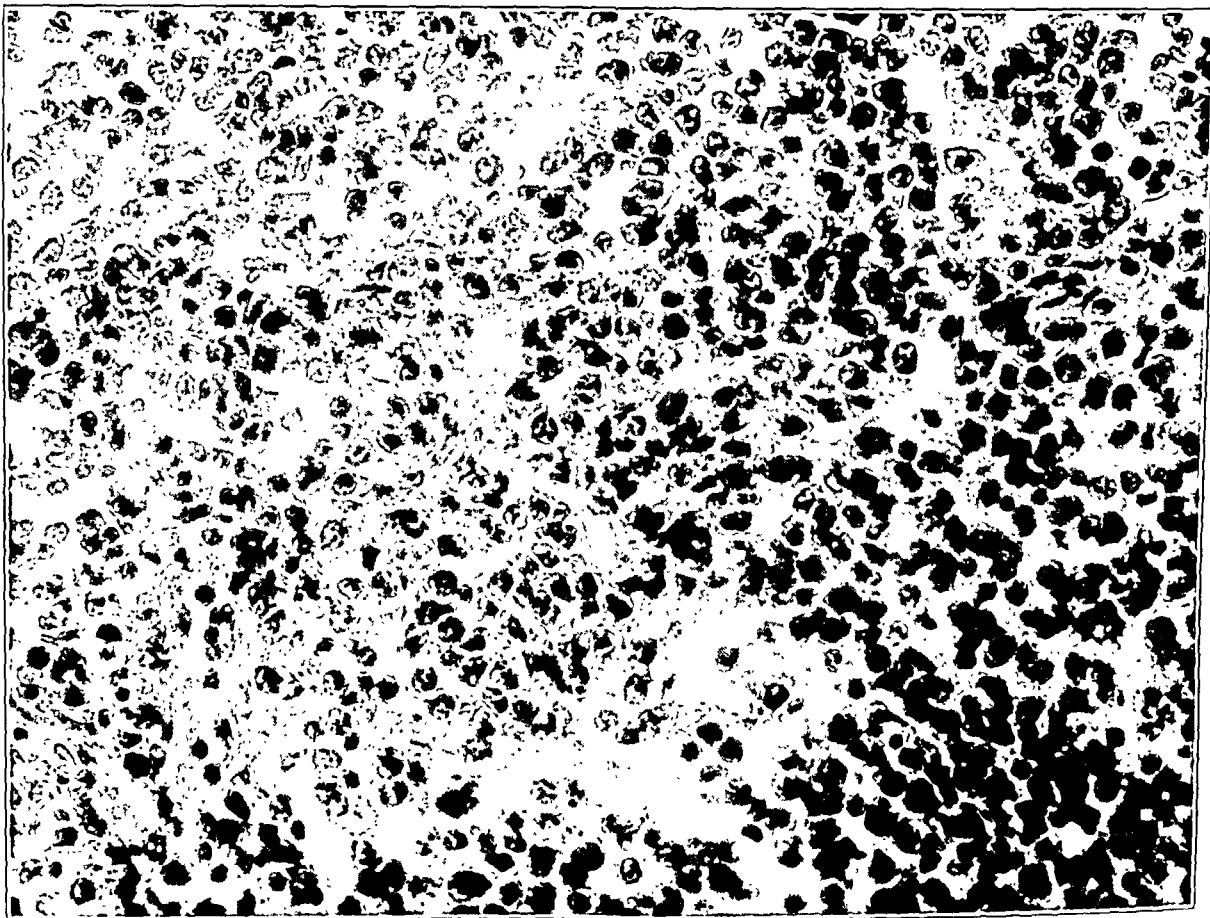


Fig. 6.—Intra-oral cancer; radiosensitive lympho-epithelioma, Schmincke type. Bulky tumors may show complete clinical regression with very little irradiation. Total sterilization requires much larger doses as a rule.

and necrosis of the bone or cartilage. Hemorrhages are rather rare. Coutard observed the development of carotid aneurysms in four patients as long as two years after irradiation. Neuritis with amyotrophic atrophy and paralysis has occurred. Sclerosis of the small bones of the middle ear, deafness and cataracts have resulted. Radiation sufficient to produce tumor regression has in some instances led to massive laryngeal necrosis some months after the irradiation. This results in

part from progressive endarteritis, especially when associated with latent infection in areas of cartilage necrosis. Coutard believes that these cartilage necroses are for the most part the result of actual invasion of the cartilage by tumor, and the experience at the Memorial Hospital points to the same conclusion.

The statement has been made that metastases of the lymph node are more radiosensitive than the primary tumors. There is no agreement among radiologists and pathologists on this point. I believe, from a

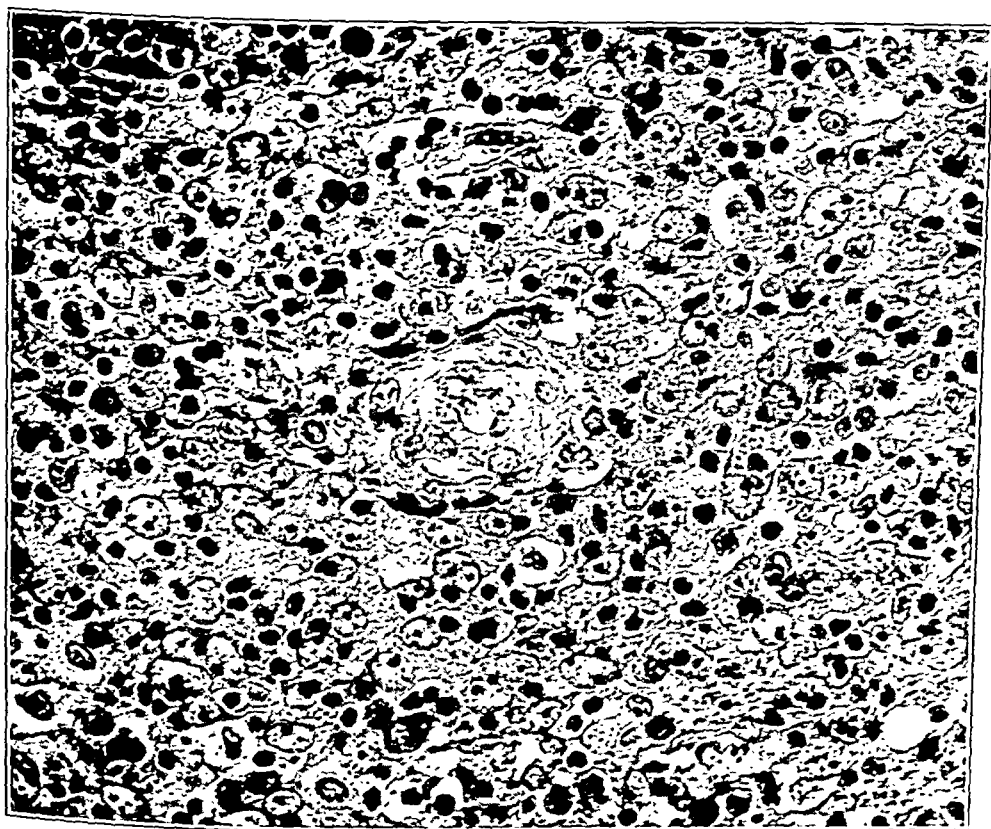


Fig. 7.—Intra-oral cancer; radiosensitive lympho-epithelioma, Regaud type.

survey of a large number of cases at the Memorial Hospital, that the sensitivity of metastases of the lymph node may be quite different from that of the primary tumor, but that it does not vary in a constant direction. Nodes may be more or less sensitive. They tend, I believe, to be slightly more resistant. In a review of sixty recent intra-oral lesions I found but two instances in which the nodes completely regressed, but in which the primary lesions persisted. There are numerous instances of regression of the primary lesions but persistence of the nodes. In each case the fact that the node contained cancer cells was shown by aspira-



tion. They were not merely hard, sclerotic nodes. Without histologic material in some abundance from the nodes of oral cancer prior to the irradiation, I doubt whether one can say why they do or do not regress. It might be interesting to compare the irradiation behavior of nodes with their known duration. It is probable that rapidly developed, more or less fulminating metastases of the lymph nodes might be more sensitive than the primary lesions. On the other hand, some intra-oral carcinomas metastatic to nodes become decidedly desmoplastic. Such nodes should be resistant. Moreover, there is a pronounced tendency for liquefaction and central sloughing with cavitation in the older nodes and rarely in the acute metastases. Such nodes might be expected to be more resistant. Lymph nodes the site of metastatic cancer undergo sclerosis under amounts of radiation which have little effect on uninvolved nodes. The normal lymph node is a radioresistant structure. When carcinoma has escaped from the confines of a node and infiltrates the fascias, it tends almost uniformly to be radioresistant despite its other histologic characteristics.

The miscellaneous tumors of the minor salivary glands, mixed tumors, adenoid cystic epitheliomas and adenocarcinomas of the intra-oral cavity are still insufficiently studied as to their behavior under irradiation. Very few are radiosensitive, and most of them possess the resistance of adult squamous cancer. At the Memorial Hospital no patients have been cured by external irradiation. Berven reported the tumors as resistant, and he has had no cures by external irradiation. Coutard regards them as resistant.

Owing to their location in bone, adamantinomas do not encourage aggressive irradiation. Irradiation as a prelude to surgical intervention appears to have little logic. The adamantinoma group is complex. In structure, the tumors vary from rather quiescent, largely cystic tumors, through the classic textbook adamantinoma, to atypical glandlike growths and tumors closely resembling squamous cancer. Their behavior under irradiation must doubtless vary with their structure, but adamantinoma is not a common tumor and observations are so far insufficient to enable one to express any opinion as to the sensitivity or resistance of given types.

#### TUMORS OF THE PAROTID AND SUBMAXILLARY GLANDS

These tumors constitute a complex group. The results of surgical removal of the relatively benign mixed tumors appear to be rather unsatisfactory. In Benedict and Meig's series, 13 of 41 patients had one or more recurrences. On the other hand, the surgical treatment of patients with true carcinomas is nearly 100 per cent disastrous. The bad results of surgical intervention even in the most competent hands

should encourage attempts at an irradiation approach to this problem. Even with the seemingly encapsulated mixed tumors it is difficult to predict the structure before operation. Many mixed tumors show areas of epidermoid carcinoma of the salivary ducts or of adenoid cystic adenocarcinoma. The former tend to recur locally and to metastasize to regional nodes. The latter may metastasize as widely as any known tumor. Their metastases to bone may be so extensive that roentgenograms will suggest multiple myeloma. I have seen an impressive number of adenoid cystic carcinomas metastasize to bone, and have seen them yield not only the usual visceral metastases, but also metastases to the spleen, pancreas, ovaries and uterus. Our patients with diffusely metastasizing tumors all had repeated surgical treatment, which may well have been a factor in the wide dissemination of the tumors.

Unfortunately, these tumors of the salivary gland are not very radiosensitive. At the Memorial Hospital some mixed tumors have yielded to interstitial irradiation and have, as shown by subsequent removal, been reduced to inert hyaline masses. In rare instances external irradiation has resulted in complete regression of what were clinically mixed parotid tumors. Complete regression of a verified mixed parotid tumor under external irradiation is a rarity. Belot and Menegaux<sup>36</sup> reported the cure of a patient with a pathologically verified, recurrent, mixed, parotid tumor by external irradiation. Wickham<sup>37</sup> described 5 successful results by surface application of radium in mixed tumors. All were in patients with residua or recurrences following surgical intervention. With 5 tumors described as "*epithéliomas de morphologie imprécise intermédiaire entre le malpighien et le glandulaire atypique se rapprochant plus ou moins de l'une ou de l'autre de ces formes*" (epitheliomas of uncertain morphology, intermediate between the malpighian and the atypical glandular forms, resembling, more or less, one or the other of these forms), he related 1 failure with combined surface and interstitial irradiation, another with surface irradiation only. 1 death from hemorrhage following combined treatment and 2 failures after surface applications. From his descriptions it is inferred that his cases of failure corresponded to the type we classify as adenocarcinoma or as adenoid cystic carcinoma. Wickham reported 1 complete regression, but the time interval is too short to call the patient cured. In a single patient with a purely "glandular epithelioma" the tumor regressed markedly, but since the patient refused to complete the treatment, the tumor rapidly recurred. From Wickham's report one would conclude that the mixed parotid tumors are more sensitive than the cellular adeno-

36. Belot, J., and Menegaux, G.: *Bull. Assoc. franç. p. l'étude du cancer* **19**: 366, 1930.

37. Wickham, Y. L.: *Bull. Assoc. franç. p. l'étude du cancer* **19**:370, 1930.

carcinomas. Balestra<sup>38</sup> stated that radiation is of considerable value in mixed parotid tumors, leading in some to complete disappearance and in others to considerable reduction in size. Apparently the complete disappearance required interstitial therapy. Schreiner and Mattick<sup>39</sup> reported the cases of 16 patients with mixed tumors who were treated by irradiation as the primary method. Of these, 3 had complete regression; 7 were clinically cured, but a hard indurated nodule remained; 1 was unimproved; 1 was lost track of, and 4 died. Of the last, 2 died of other causes. None of these patients was treated with external irradiation, yet the series shows that a fair proportion of mixed parotid tumors is sufficiently sensitive to yield to interstitial irradiation. Benedict and Meigs<sup>40</sup> did not speak enthusiastically of radiation. On the other hand, no evidence is presented in their paper that any irradiation program designed along modern physcobiologic lines to effect a cure by radiation had been adopted. Their figures are illuminating from the point of view of prognosis after purely surgical intervention. Taken as a whole (all tumors of the major salivary glands included), recurrences after surgical intervention average about 50 per cent. Of 18 sarcomas, 17 were fatal, and 1 patient was alive with disease. One must question the diagnosis in any such number of sarcomas. Were not many of them myxosarcomatous in structure and hence clearly epithelial according to the modern concept of metaplasia in the salivary gland group? Of 20 patients with carcinomas, 18 died of the disease, 1 died with the disease still present, but of another cause, and 1 was alive three years without evidence of tumor. Of 41 patients with mixed tumors, 13 had recurrences after surgical intervention, several being multiple recurrences. The results are far from encouraging.

It would appear that the less malignant tumors of the salivary gland, the mixed tumors in contradistinction to the adenocarcinomas, are the more amenable to radiation. From their structure one would not assume this to be the case. The adenocarcinomas are more cellular; their cells are smaller and more closely packed, and their blood supply appears less stable. The behavior of the mixed tumors is probably related to their natural history. They tend to grow slowly; periods of quiescence alternate with periods of growth. Certain of them appear self-limited. Surgical statistics seem to indicate that even the rupture of these tumors with spilling of contents at the time of operation does not necessarily lead to recurrence. Their tendency in many cases to regress under irradiation is probably the result of chronic "discouragement" of cells the neoplastic properties of which are by no means always aggressive.

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38. Balestra, G.: *Radiol. med.* **16**:574, 1929.

39. Schreiner, B. F., and Mattick, W. L.: *Am. J. Roentgenol.* **21**:541, 1929.

40. Benedict, E. B., and Meigs, J. V.: *Surg., Gynec. & Obst.* **51**:626, 1930.

The submaxillary salivary tumors are almost always true aggressive carcinomas and are highly malignant. They are not radiosensitive, and treatment by any means seems unsatisfactory.

#### CARCINOMA OF THE NASAL MUCOSA AND SINUSES

Many carcinomas of the mucous membrane of the nose and nasal accessory sinuses are radiosensitive. Markedly sensitive epidermoid carcinomas exhibit the structure of transitional carcinoma or of lympho-epithelioma. Schneiderian carcinomas, if decidedly anaplastic, are radiosensitive. When they contain much mucus they are radioresistant. These radiosensitive tumors of the nasal mucosa and sinuses are apt to recur with great rapidity after an initial pronounced regression. When they metastasize to nodes, the nodes are sensitive. Their tendency to metastasize is not as great as their high cellularity might lead one to anticipate. When they do metastasize, they are apt to spread widely and yield distant visceral metastases. Many remain local and cause death by hemorrhage, sepsis and erosion of the regional bony structures.

Radioresistant squamous carcinomas develop either locally or on the basis of a diffuse polyposis of the mucosa of the nose or sinuses. Epidermoid carcinomas of varying structure may develop in the region of the ethmoid cells. They have not been sensitive tumors. Interstitial irradiation has resulted in meningitis. Carcinomas of the mastoid cells have been extremely difficult irradiation problems owing to their location in bone. There exists, however, a small group of anaplastic tumors with decidedly embryonal cells. These lesions occur in children. They may first present themselves in the mastoid area, although they seem to arise primarily in the region of the tonsil or the eustachian tube. They are extremely radiosensitive.

Certain vascular papillary or polypoid tumors of the nasal region variously classed as angiofibromas or angiosarcomas, although not radiosensitive in the usual sense, may nevertheless undergo slow sclerosis after repeated irradiation. Portmann, Bonnard and Moreau<sup>41</sup> have described a radiosensitive tumor of the nasal region under the term "esthesioneuroblastome." It is said to arise from neuroblastic cells and is hence quite distinct histogenetically.

#### CARCINOMA OF THE LUNG

Primary bronchogenic carcinomas often show a structure which would lead one to believe they were radiosensitive. This is especially true of the so-called oat cell carcinomas. Despite this fact irradiation of cancer of the lung has been on the whole unsatisfactory. There is

41. Portmann, Bonnard and Moreau: *Acta oto-laryng.* 13:52, 1928.

little evidence that it prolongs life in the majority of cases. At the Memorial Hospital there is but a single patient with proved bronchogenic carcinoma alive, but with disease, five years after treatment was instituted. I have witnessed pronounced regression of anaplastic carcinoma of the mucous glands. Most radiologists find little cause for elation in the therapy of cancer of the lungs. Paterson,<sup>42</sup> in 19 cases, found no prolongation of life, but noted temporary improvement in all but advanced tumors. On the other hand, Leddy and Vinson<sup>43</sup> have quite recently reported definite palliative results. Of 42 patients treated, 10 were living from fifteen months to four years after a diagnosis of bronchogenic carcinoma was made. Thus, it would seem that a certain number of such tumors are sufficiently radiosensitive to permit of definite palliation.

#### CARCINOMA OF THE ESOPHAGUS

Epidermoid carcinomas of the esophagus form another discouraging field for the radiologist. Few show a structure suggestive of radiosensitivity, and in these there is little actual proof that they behaved like sensitive lesions. In fact, in a large series of esophageal lesions I have seen much more evidence of actual irradiation effect, histologically, in the relatively adult squamous carcinomas, in which the treatment may result in increased cornification, degenerative hyalinization, abortive atypical mitotic divisions and ballooning degeneration of tumor cells. There is a great variation in the effect of the radiation on different tumors of seemingly similar histologic structure. Naturally, the dose that can be administered to these tumors does not approach that which is known to be effective on other epitheliomas of the same type. Neither does it appear that the degree of regression observed with the very cellular tumors of the oropharynx is approached in the case of esophageal lesions of similar structure with the same dosage. The esophagus is a thin-walled viscus. Many of the tumors are outside the esophagus when first seen, adherent to adjacent structures, and are already ulcerated and desmoplastic. The patients are often greatly emaciated and anemic and are unsatisfactory subjects for irradiation. I have the impression that the glandular tumors of the lower part of the esophagus or cardia, so situated that they obstruct the esophagus, are slightly more sensitive, although my experience is slight with this variety. In the case of a patient with this type of lesion treated recently at the Memorial Hospital, ability to swallow was regained in part, and the patient gained 18 pounds (8.2 Kg.) in a few weeks. The dose employed was much larger than the usual one and of such magnitude

42. Paterson, Ralston: *Brit. J. Radiol.* 1:90, 1928.

43. Leddy, E. T., and Vinson, P. P.: *Proc. Am. Roentgen Ray Soc.*, 1932.

that probably few patients would have tolerated it. The same degree of palliation might possibly have been attained by dilation alone.

Zuppinger<sup>44</sup> has recently expressed the opinion that esophageal carcinomas should be a relatively favorable type for radiation, since for the most part they are epidermoid in structure (*Pflasterzellkarzinome*), in a measure radiosensitive as opposed to glandular carcinomas. The author discussed his technic and reported the cases of 4 patients treated by his methods. Aside from the assumption that the epidermoid tumors are more sensitive than the glandular growths, Zuppinger has nothing to say regarding specific radiosensitivities. In fact, if one judges by the case reports in the paper, glandular tumors (*carcinoma cylindrocellulare adenomatosum* and *carcinoma solidum simplex et colloides partim adenomatosum cylindrocellulare*), actually gave better responses to radiation than did the epidermoid tumors, thus seeming to offer denial to Zuppinger's original premise. He concludes with the statement that the histologic findings are a guide to the choice and amount of treatment, although precisely how that conclusion can be drawn from the subject matter of his paper I am unable to state.

I am inclined to question clinical evidence that glandular carcinoma of the cardia is either more or less sensitive than epidermoid cancer of the esophagus. Much of the symptomatology of carcinoma of the cardia depends on actual obstruction, whereas in the esophagus the presence of ulceration markedly interferes with the function of an organ the seat of a vigorous peristaltic wave motion. Wholly different mechanisms may well be the basis for clinical alterations following irradiation, and unless one has a rather broad concept of what is meant by radiosensitivity, the matter appears too vague to discuss.

#### CARCINOMA OF THE STOMACH, COLON AND RECTUM

The epithelium of the stomach is not very radiosensitive. Of the gastric glands, those of the pyloric region appear most resistant. The peptic glands are less so. Both parietal cells and chief cells are moderately sensitive, especially the latter (Regaud and Lacassagne<sup>45</sup>). The epithelium of the intestinal villi and that of the glands of Lieberkühn are relatively sensitive. For a description of the irradiation of lesions of the gastro-intestinal tract, the reader is referred to the paper of Regaud, Nogier and Lacassagne.<sup>45</sup>

Unfortunately, the comparative sensitivity of certain portions of the gastric mucosa seems to have little bearing on the behavior of gastric cancer. Radiosensitive gastric cancers are rare. Furthermore, there is

44. Zuppinger, A.: *Strahlentherapie* 28:639, 1928.

45. Regaud, C.; Nogier, T., and Lacassagne, A.: *Arch. d'électric. méd.* 20: 321, 1912; *Paris méd.* 8:489, 1912.

essentially no information available on the relation between tumor structure and the rare favorable response to radiation. Occasional encouraging results of irradiation have been obtained in several clinics (Holfelder,<sup>46</sup> Schmidt,<sup>47</sup> Werner<sup>48</sup> and others). At the Memorial Hospital I have seen a few palliative results and an apparent cure, now of nearly four years' duration. This patient had a bulky inoperable lesion filling the fundus and obstructing the cardia. She was subjected to laparotomy, and a biopsy specimen was obtained. The microscopic diagnosis (Ewing) was a cellular, small cell, diffuse carcinoma. Under irradiation the mass completely vanished, and the patient remains well. Personally I am not wholly satisfied that the tumor is not a gastric lymphosarcoma. I have observed other favorable, but only palliative, results with tumors of the cardia. It is interesting to note that Holfelder, ten years ago, stated that carcinomas of the cardia and lesser curvature were more favorable for irradiation, although he based his statement on technical grounds. He saw no means of predicting irradiation behavior from the gross form or microscopic structure of the tumors.

Schmidt reported the results of irradiation in 30 cases of gastric cancer. Only 1 highly favorable result was obtained. Twenty-one of the patients died, and 8 were lost sight of. Twenty-nine of the 30 were inoperable cases; the other was a postoperative recurrence. Schmidt is frankly pessimistic even as regards the apparent cure. He stated:

Mag der eine oder der andere Fall radiosensibler sein und die Ursache nach Analogie anderer Tumoren in biologischen Eigentümlichkeiten (regere Zellteilung?) zu suchen oder mag es sich in unserm Fall um eine der seltenen Remissionen gehandelt haben, die nicht durch die Strahlentherapie hervorgerufen sind, auf jeden Fall ist das Fazit aus unseren bisherigen Bestrahlung so wenig ermutigend, dass wir nach dem heutigen Stand der Dinge mit Jüngling nicht einmal das inoperable Magencarcinom systematisch bestrahlen. (May certain cases be more radiosensitive, and may the cause, by analogy with other tumors, be found in biologic peculiarities [more active cell division?], or may our case have been one of the rarely occurring remissions that are not produced by ray therapy; at any rate, the conclusion derived from our irradiation up to now gives little encouragement, so that on the basis of the present status of the matter we agree with Jüngling and do not employ systematic irradiation even in inoperable carcinoma of the stomach.)

With the exception of a few bulky, cellular, papillary adenocarcinomas of the cecum, the carcinomas of the large bowel appear radio-resistant. Rectal carcinomas vary greatly in their sensitivity. Lacassagne<sup>49</sup> found the majority of them resistant. In reviewing

46. Holfelder, H.: *Strahlentherapie* 15:715, 1923; 42:497, 1931.

47. Schmidt, Walter: *Strahlentherapie* 30:197, 1928.

48. Werner, R., in Gauss, C. J., et al.: *Lehrbuch der Strahlentherapie*, Berlin, Urban & Schwarzenberg, 1925, vol. 2.

49. Lacassagne, A.: *Radiophys. et radiothérapie* 2:577, 1932.

sections on several hundred rectal cancers, I find that I am unable save rarely to predict the behavior of a rectal carcinoma to radiation. The stenosing fibrocarcinomas are certainly radioresistant. The colloid carcinomas are resistant. Very cellular, solid, infiltrating carcinomas with essentially no glandular structure often regress, but tend to recur rapidly in a few months. Adenoma destruens varies markedly in its behavior. Radiosensitivity has been noted especially with papillary glandular tumors composed of peculiarly delicate-looking, hydropic cells resembling embryonal cells. There is little in the histology of rectal cancer which would lead one to suspect radiosensitivity. In fact, usually all the features point to a resistance-glandular origin: the presence of secretion, desmoplastic features in tumors of fair duration, pronounced fibrosis in the stenosing types, ulceration and deep infection. Despite years of effort in the direction of cure of rectal cancer by radiation, successes are few. At the Memorial Hospital it is the feeling that operable rectal cancer is usually a surgical problem unless the tumor is small and readily accessible. Binkley<sup>50</sup> has 22 patients well from two to seven years after irradiation or irradiation plus colostomy. In most instances it must be understood that rectal cancer is cured not because it is radiosensitive, but because it has been subjected to caustic interstitial irradiation. Perhaps the majority of rectal cancers are sufficiently sensitive to permit considerable palliation by external irradiation. Palliation consists in reduction in the size of the tumor, cessation of mucous discharges and hemorrhage, diminution in ulceration and relief of pain. These facts are common knowledge in all radiologic centers. At the Conference on Cancer held in London in 1928, successive reports were made by Lockhart-Mummery,<sup>51</sup> Quick,<sup>52</sup> Neuman and Coryn,<sup>53</sup> Hartmann<sup>54</sup> and Gordon-Watson.<sup>55</sup> To me the tone of these papers is rather discouraging. In a later paper, Gordon-Watson, although expressing himself with considerable caution, concluded that "although there is little hope for a patient under thirty, afflicted with rectal cancer, however treated, he has more chance of cure with radium than with surgery. . . . The more active the growth the more radiosensitive

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50. Binkley: Personal communication to the author.

51. Lockhart-Mummery, J. P.: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 117.

52. Quick, Douglas: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 125.

53. Neuman, F., and Coryn, G.: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 128.

54. Hartmann, Henri: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 167.

55. Gordon-Watson, Charles: Report of the International Conference on Cancer, New York, William Wood & Company, 1928, p. 169; *Ann. Surg.* 92:467, 1931.



it is." Our best temporary regressions under external irradiation have been in cellular tumors in young subjects.

The situation is quite different in the case of epidermoid carcinomas of the anal canal. These tumors exhibit the usual sensitivity of epidermoid carcinomas elsewhere. Of the miscellaneous gastro-intestinal tumors, the lymphosarcomas, leukemic lymphomas and aleukemic lymphomatous tumors are radiosensitive. The melanotic tumors are extremely resistant. Nothing is known of the behavior of the rare myosarcomas, nor of the benign carcinoids which occasionally yield metastases.

#### CARCINOMA OF THE BREAST

Cancer of the breast is not a single anatomic disease, but consists of a group of related pathologic entities which behave clinically different and which show differences in their response to radiation. Most cancers of the breast are relatively radioresistant. As a general rule, it may be stated that the quantity of radiation delivered in most instances to any cancer of the breast by the external radiation so far employed is insufficient to control the disease. Calculated in terms of interstitial radon, the dose required to sterilize the average cancer of the breast appears to be in the neighborhood of 10 skin erythema doses. This would, of course, seem to make interstitial treatment imperative. Delivered by diffuse external irradiation, the dose necessary is certainly less, and it is our opinion that the possibilities of external irradiation in the control of cancer of the breast have scarcely been touched.

Undoubtedly a certain number of carcinomas of the breast are so situated and of such size that they may be successfully attacked by radiation with interstitial radon. They are sufficiently sensitive to yield to such radiation in quantities insufficient to cause normal tissue slough. Yet I am not impressed with interstitial radon seeds in cancer of the breast. For the most part, the tumors are so resistant and the chances of accurate seed placement are so hazardous that the irradiation effect is spotty. In a number of cases so irradiated I have seen great irregularities in the effect on the tumor. Areas of total irradiation necrosis alternate with others where I can see little effect of the radiation and where the tumor cells appear fully viable. The reactive fibrosis is likewise irregular and often abortive. Most of these tumors were studied by large Cheatele sections, giving an excellent survey of the whole local process. Even when the clinical evidence points to a remarkable shrinkage in the size of the palpable lesion viable cells may still appear microscopically. They may also appear, as is well known, in clinically quiescent lesions in patients who have passed the five year period.

The spotty character of interstitial seed radiation appears particularly in the axilla. I have never seen satisfactory irradiation of axillary nodes by this method. On the other hand, the reports of Geoffrey

Keynes<sup>56</sup> on the use of long radium needles are impressive to say the least. Attempts to duplicate Keynes work, with radon wires instead of needles, have not yielded histologic results that impress me, although several excellent clinical regressions have occurred. In the earlier cases the patients received too heavy a dose. An attempt to follow this treatment by radical surgical intervention led to serious necroses of the wall of the chest. Apparently when sufficient radon has been administered to destroy completely a large resistant cancer of the breast, the local tissues are so damaged that additional interference with the blood supply in the course of a mastectomy tends to produce sloughing of the wall of the chest and prolonged infection. In some instances the paralysis of

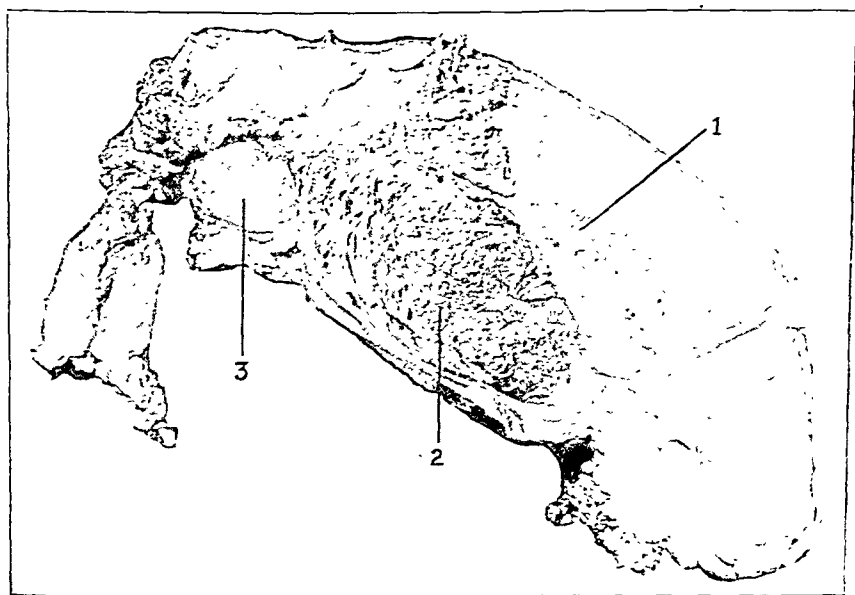


Fig. 8.—Carcinoma of breast: 1 indicates an infiltrating large cell duct carcinoma; 2, an intracystic papillary adenoma malignum; 3, a metastatic deposit in the axilla containing both histologic types.

reactive tissues is such that cancer has recurred exuberantly in the wall of a foul irradiation ulcer. The average mammary cancer is so resistant that I personally doubt the feasibility of attempting complete destruction by interstitial irradiation unless the lesion is small and accessible.

Interstitial irradiation of a large tumor can yield little or no information on the sensitivity of different types of cancer of the breast. One must depend for information on the behavior under adequate amounts of external irradiation, i.e., a diffuse uniform source of energy and not irregular, scattered, caustic radiation. Under those circumstances

56. Keynes, Geoffrey: *Brit. J. Surg.* 19:415, 1932.

one may observe wide differences in behavior and, unfortunately, differences which are not easily related to structural type, although I believe well defined tendencies toward constant behavior may be noted. There exists first the bulky adenoma malignum or adenocarcinoma developing in cysts or dilated ducts (figs. 8, 9 and 10). This tumor may long maintain its encapsulation and grow to large size and show marked cellularity without involving the axillary nodes. There is a pronounced tendency to undergo spontaneous infarction. This ten-

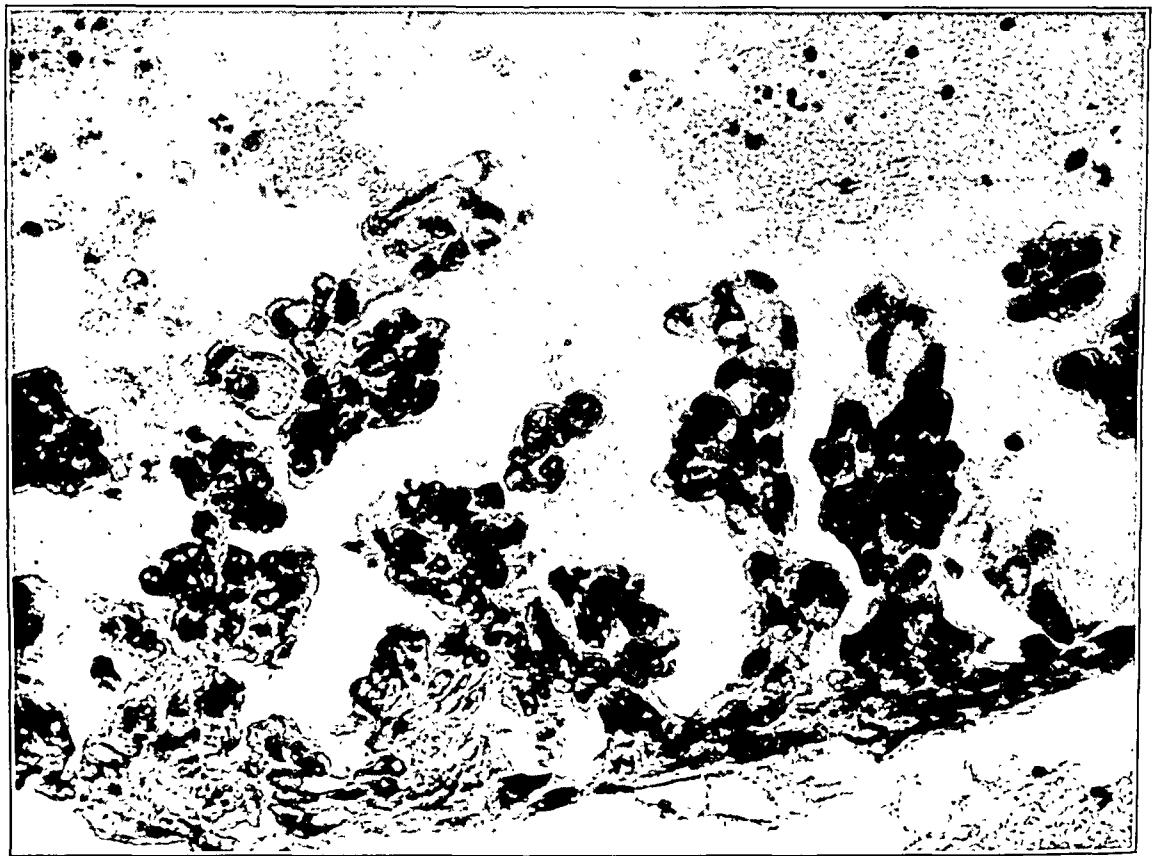


Fig. 9.—Radiosensitive carcinoma of breast. Its relative sensitivity is dependent on its papillary character and blood supply (region 2 of fig. 8).

dency is accentuated by irradiation. These tumors regress under irradiation, yet there is evidence that the effect is not on the tumor cells but on the blood supply. Once outside their capsules and hence less susceptible to infarction, these tumors are radioresistant. The less cellular tumors, particularly those with well developed glands and little removed from benign intracystic adenomas, undergo chronic sclerosis and calcification under irradiation. When subsequently excised, they are apt to show atrophy of the cells, pronounced hyaline thickening of their vessel walls, obliteration of the vessels with calcification and deposits of calcium in necrotic tufts of tumor cells.

Comedocarcinomas are apt to be moderately radiosensitive when confined to ducts. They undergo necrosis, and masses of sloughed tumor cells impregnated with calcium replace the active process. When a comedocarcinoma infiltrates beyond the wall of the duct, the infiltrating portions are readily seen to be much less sensitive.

There is a type of cancer of the breast which originates in multiple foci throughout the whole duct system or which spreads diffusely

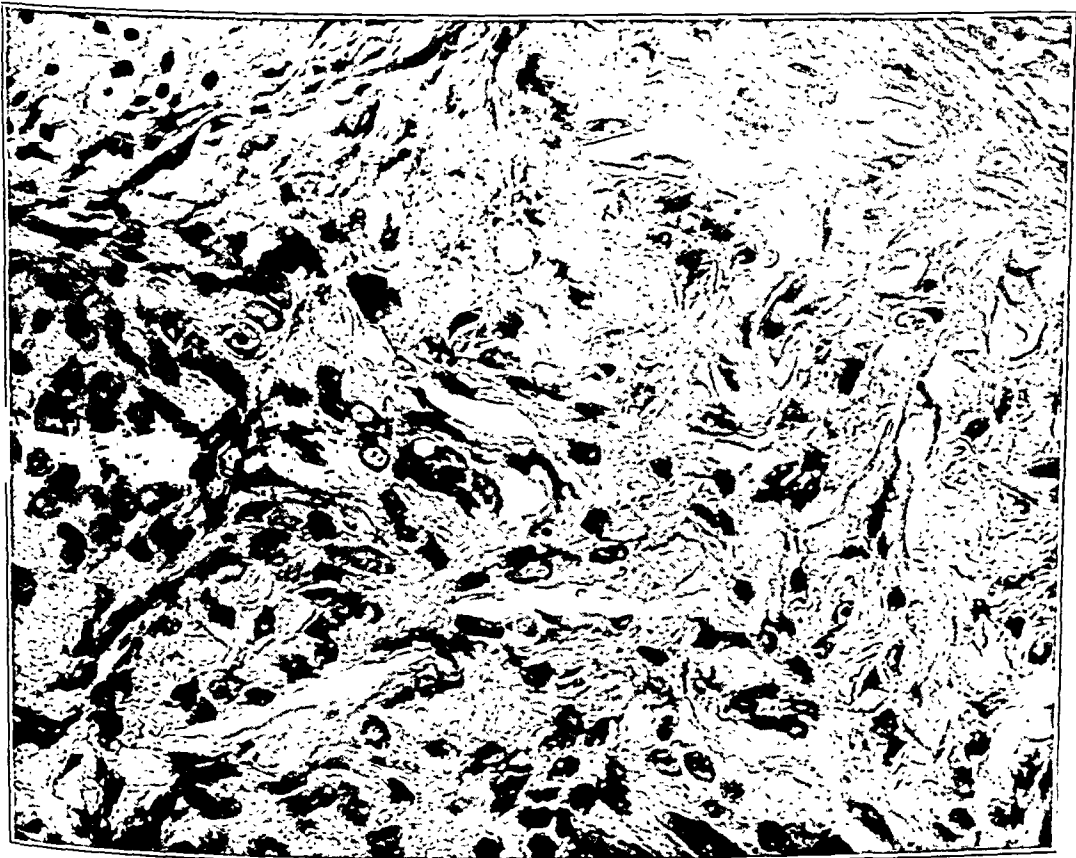


Fig. 10.—Large cell infiltrating duct carcinoma; radioresistant (region 1 of fig. 8).

through the entire duct apparatus of the breast (fig. 11). This type, when seen "early," gives the clinical picture of an ill defined diffuse induration. The breast is usually large and fat. A pig-skin appearance is often a prominent feature. The skin is often thickened, and inflammatory features are relatively common, although it is known that "inflammatory carcinoma" does not necessarily mean any specific morphologic type. The entire breast may be edematous. The edema is presumably due to a diffuse plugging of periductal lymphatics by

tumor cells. Whereas much of the duct system may be involved by cancer, these breasts are sometimes difficult to recognize as cancerous in the gross. The appearance is usually that of a diffuse fibrous mastitis. The presence of rather too much induration, the diffuse dimpling of the skin, the large fat lobules, which usually bulge on section as if relieved from restraining fibrosis, and especially a fine nodularity of the duct system should lead to the diagnosis of this type of cancer of the breast. Definite tumor masses may be a late occurrence, and by the time these occur the breast usually tends to be smaller than the



Fig. 11.—Bilateral diffuse duct cancer. Right breast, infiltration limited to periductal lymphatics; relatively sensitive; left breast, later stage with much infiltration, formation of bulkier masses, fibrosis and retraction; resistant.

opposite organ, although the high fat content impedes contraction. These diffuse duct cancers are usually radiosensitive, and after external irradiation it may be extremely difficult to detect cancer in the amputated specimen. In one instance, after rather moderate irradiation, I searched through 20 suggestive areas microscopically before finding a few atrophic cancer cells. When definite masses are present, the irradiation effect is much less, and I know of no evidence to show that the lymphatic extensions of this type of cancer behave any differently from others. Any precise explanation for the observed sensitivity of this type is lacking. It must be remembered that the tumor infiltration outside of the ducts

and periductal lymphatics is slight. The tumor cells occupy narrow strands 1 or 2 cells thick. Their blood supply has not gone far toward established autonomy. The irradiation results in a marked increase in the edema, which, as has been stated, is often present before treatment. This may be the result of swelling of tumor cells within the plugged lymphatics. This edema may in a measure interfere with cell-fluid exchanges and lead to intoxication, thus rendering the tumor cells more vulnerable to the radiation. As usual, one must differentiate between sensitivity and cure. These tumors are not curable by surgical

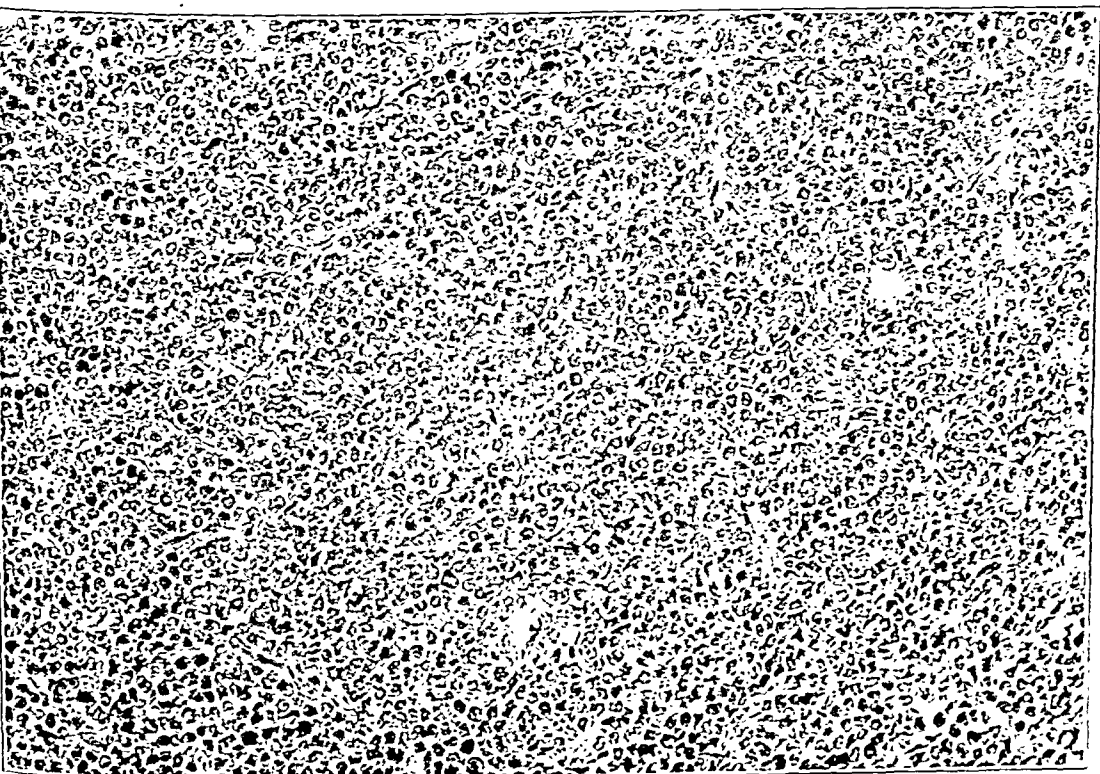


Fig. 12.—Radiosensitive small cell solid duct cancer of breast.

intervention, nor have they been cured by radiation. They metastasize early and diffusely.

Knox<sup>57</sup> expressed the belief that there is reason to think that the more differentiated cancers of the breast are more susceptible to radiation. This accords with my own belief as regards the intraductal adenocarcinomas and the comedo types. I believe that there is a group of small cell, diffusely infiltrating, highly malignant duct cancers which are apt to be highly sensitive (fig. 12). They yield rapid, diffuse meta-

57. Knox, L. C.: *Radiology* **11**:220, 1928.

stases, and I believe them unsuited for surgical intervention. Outside of the types mentioned I cannot predict the radiation behavior of cancer of the breast with any degree of accuracy. I am usually more surprised at the regressions than at the failures to secure regression. One fact impresses me strongly and that is that, provided the tumors are not too large, infected, desmoplastic or fixed to surrounding structures, the radioresistance diminishes as one approaches a reasonable dose. This dose is not that attained by the usual breast "cycle." External irradiation can make little progress in cancer of the breast so long as the radiologist must leave the area of skin in condition to withstand radical mastectomy.

Regression of axillary disease is often excellent. I have seen the most satisfactory regressions after treatment through 5 portals, delivering about 550 roentgens each. The nodes may disappear or undergo extreme fibrosis. They are replaced by finer or coarser collagen fibers, and the lymphoid tissue is greatly reduced. We have seen the beginning of fibrosis twenty-one days after irradiation. It originates in the perivascular region of the trabeculae, although at this stage the vessels themselves appear unaltered. Capsular fibrosis is just beginning. The fibrosis appears in regions of the node involved by cancer and to not nearly the same extent in uninvolved regions. Residual tumor cells appear small, atrophic, hydropic and isolated in fibrous tissue. The process is one of early abortive fibrosis. These results in the axilla equal the best I have ever seen by interstitial irradiation of the breast itself, and are vastly better than anything previously observed in the axilla after interstitial irradiation given in this hospital. Nodes which contain cancer undergo pronounced sclerosis after doses that are tolerated without perceptible effect by normal or hyperplastic nodes (figs. 13 and 14). The normal lymph node is a relatively resistant structure. The 5 portal method has given several excellent clinical regressions of axillary disease in addition to those actually observed in specimens after operation. I have been much encouraged with these results, and am of the opinion that, were this type of radiation developed to a maximum of efficiency—perhaps with variations in quantity and time factors—much more might be accomplished in the axilla. We have seen similar histologic pictures in axillary nodes after a 3 portal irradiation. The tumor received about 130 per cent skin erythema dose. With this dose effective in the axilla, it seems extraordinary that any average primary tumor of the breast should require in the neighborhood of 10 skin erythema doses for adequate sterilization. There is something "spotty" about the effect of interstitial irradiation by radon seeds in cancer of the breast which does not appeal to us. It must mean merely that such tumors are difficult to outline with accuracy. Because axillary nodes

disappear with irradiation, we do not believe that the patient becomes a fit subject for radical surgical intervention.

The effect of irradiation on mammary cancer is similar to that on other relatively resistant tumors. Interstitial treatment produces necrosis of tumor cells, karyorrhexis, giant atypical nuclei, atypical mitoses, atrophy, hydropic degeneration, acute capillary necrosis, hemorrhage, eventual obliterative arteritis, fibrosis, hyalinization of the stroma, calcific deposits and the whole gamut of changes ascribed to irradiation.

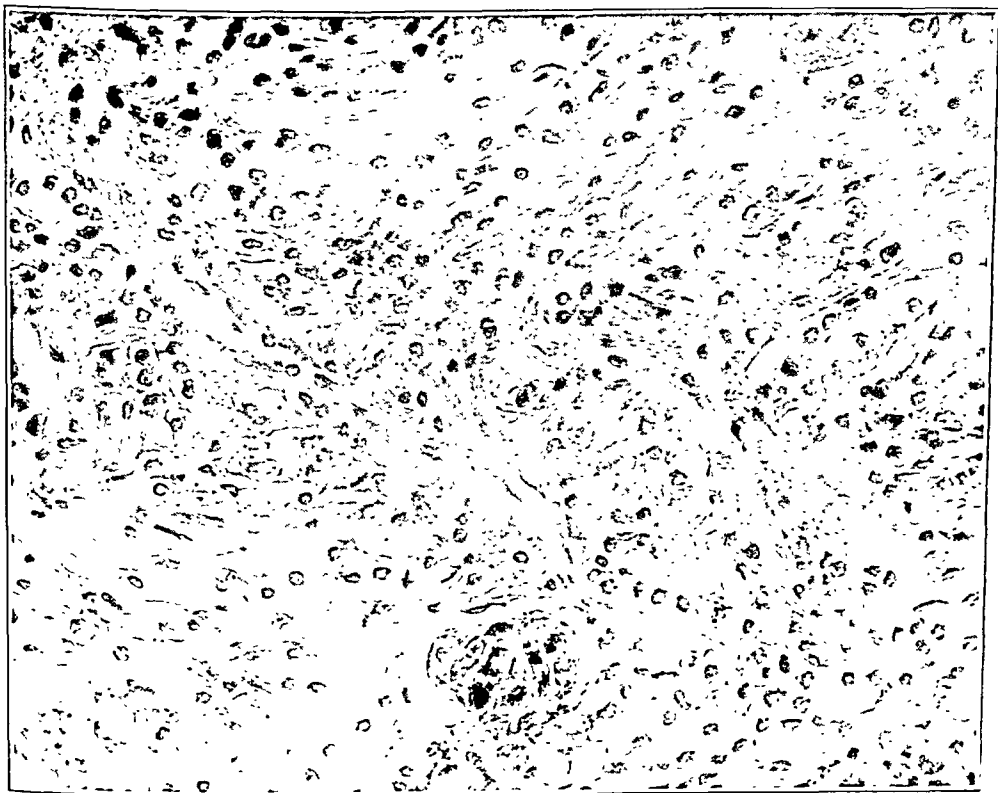


Fig. 13.—Axillary node, cancer of breast; residual atrophic tumor cells after relatively heavy external radiation.

External irradiation produces cell degeneration to a lesser degree (naturally since the doses have been smaller). The changes in the cells after external irradiation are mainly atrophy and hydropic degeneration. Obliterative arteritis from external irradiation is marked and is an important factor in restraint of growth, probably the most important in resistant tumors of the breast. After interstitial irradiation there may occur a curious squamous metaplasia of ducts and acini of adjacent lobules of the breast. Because small tumors remain palpable in the heavily irradiated breast, this is no positive evidence that they remain



capable of further damage. Many writers have found atrophic tumor cells in tumors of the breast (and in other tumors) which were clinically cured.

No discussion of the radiosensitivity of carcinoma of the breast would be even partially complete without noting the sensitivity of many dermal and skeletal metastases. There appears to be little relation between the sensitivity of a dermal metastasis and the behavior of the

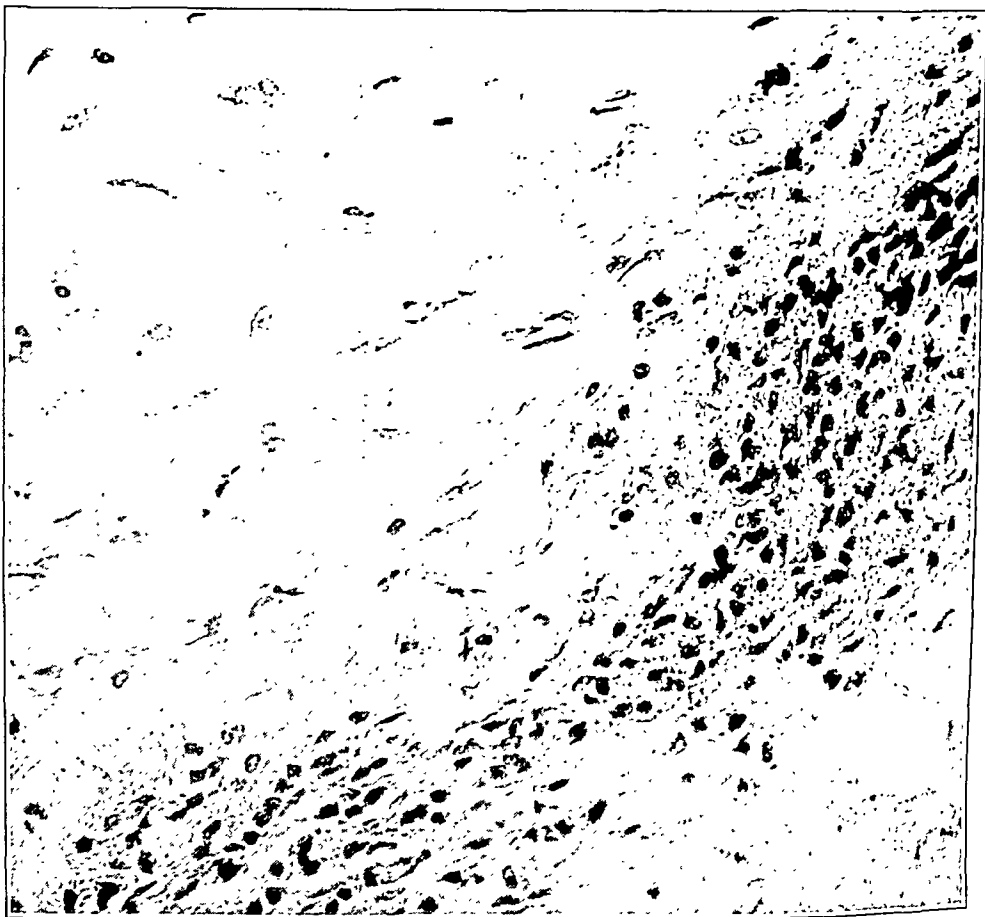


Fig. 14.—Axillary node, cancer of breast; complete sclerosis after external radiation.

original tumor of the breast. The skeletal metastases of cancer of the breast are an exception to the rule that a bony bed is an unfavorable site for irradiation of a tumor. Skeletal metastases from cancer of the breast often act exceedingly well. Pain is favorably influenced over long periods. Pathologic fractures tend to unite (they may also unite without radiation), and there may be evidence of marked roentgenographic repair. It is interesting to compare the behavior of the skeletal metastases of cancer of the breast with those of

prostatic cancer—both glandular carcinomas of the average sensitivity of glandular cancers. The latter usually yield disappointing results. The pulmonary metastases of carcinoma of the breast are but rarely influenced by radiation. In some instances it is probable that the rate of accumulation of pleural exudates is lessened.

Although no sufficient series of cases is available for conclusions, it appears probable that the radiosensitivity of certain carcinomas of the breast in young women is increased following roentgen castration. In fact, in such cases improvement may be noted without irradiation of the tumor itself. The influence of the ovary on the physiology of the breast and on the genesis of cancer of the breast has been admirably discussed by Taylor<sup>58</sup> in a recent review.

#### CARCINOMA OF THE CERVIX

There are marked divergences of opinion concerning the radiosensitivity of different types of cancer of the cervix. Healy and Cutler<sup>59</sup> have stated that the sensitivity increases with the degree of anaplasia; the adult squamous cancers are the most resistant of the epidermoid group. The moderately differentiated epidermoid carcinomas, which they designate as plexiform epidermoid carcinomas, are more sensitive, and the very cellular anaplastic epidermoid carcinomas exhibit the most pronounced degree of sensitivity. Their conclusions were that the combination of degree of malignancy and radiosensitivity was of considerable prognostic significance as regards cure. Reports from other clinics are at marked variance with this belief. Döderlein, Döderlein and Voltz,<sup>60</sup> in 1926, offered some evidence which lends support to this concept. They reported that of the cases of epidermoid carcinoma of the cervix in which cures were obtained, 10 per cent were adult carcinomas (gutgereifte Karzinome), 34 per cent were of the intermediate type (mittelgereifte Karzinome), and 56 per cent were undifferentiated (unreife Karzinome). In 1930, G. Döderlein<sup>61</sup> expressed himself with some caution on the subject:

Der Reifegrad der Carcinome scheint aber immerhin einer der Punkte zu sein, die für die mehr oder minder gute Wirksamkeit der Bestrahlung verantwortlich zu machen sind, *wenn auch noch zahlreiche andere uns bisher unbekannte Faktoren ausser dem Reifegrad hierbei noch eine bedeutende Rolle spielen* (italics mine).

58. Taylor, H. C., Jr.: The Etiology of Neoplasms of the Breast: With Notes on Their Relation to Other Tumors of the Reproductive System, Arch. Surg. **21**:597 (Oct.) 1930.

59. Healy, W. P., and Cutler, Max: Am. J. Obst. & Gynec. **16**:15, 1928.

60. Döderlein, Albert; Döderlein, Gustav, and Voltz, Friedrich: Acta radiol. **6**:335, 1926.

61. (a) Döderlein, Gustav: Strahlentherapie (supp.) **13**:21, 1930. (b) Voltz, Friedrich: *ibid.*, p. 128.

(The degree of maturity of carcinomas seems to be still one of the factors that are to be made responsible for the greater or lesser efficacy of the irradiation, even if there are numerous other, still unknown factors, besides the degree of maturity, which play an important rôle.)

In another portion of the same article, Voltz<sup>61b</sup> stated that the results of irradiation on cancer of the cervix are dependent on variations in radiosensitivity perhaps related to differences in the degree of ripeness (Reifegrad) of the tumors. In 1931, G. Döderlein<sup>62</sup> reversed his previous opinion and concluded that the degree of differentiation had little to do with cure by irradiation.

Lacassagne<sup>63</sup> found rather small differences in the behavior of different types of epidermoid carcinoma of the cervix. He stated that an investigation of the relative frequency of cures in the squamous (Plattenepithel) and transitional (Übergangsepithelcarcinome) types shows a higher percentage of successes in the squamous forms and hence a lower sensitivity in the transitional variety. After all, Healy and Cutler did not claim a higher percentage of cures in the plexiform or transitional carcinomas. Their cures were much lower. They did not relate the fewer cures to a lack of sensitivity but to a greater tendency to metastasize. Lacassagne expressed the belief that the majority of carcinomas of the cervix show a high degree of radiosensitivity. He found that the number of mitoses and the relationship of stroma and the blood vessels give no added information on the probable behavior to radiation. Warren<sup>64</sup> stated that grade II carcinomas of the cervix respond best to radiation. Thus, from different radiologic clinics there are all possible differences of opinion. The one fact on which all seem to agree is that adenocarcinomas of the cervix are radioresistant to a high degree.

I do not see how the matter of the relative radiosensitivity of epidermoid carcinomas of the cervix can be decided with certainty on the basis of present methods. The statements as to the differences in sensitivity made by Healy and Cutler were after all based more on analogy than on observations. In estimating the sensitivity from histologic features the authors drew conclusions from the known behavior of epidermoid carcinomas in other locations, reactions of tumors similar in structure to cancer of the cervix. There are numerous difficulties in the study of the sensitivity of cancer of the cervix. First is the matter of dosage.

The cervix itself is sufficiently radioresistant to tolerate enormous doses. In the physics department of the Memorial Hospital the dosage received by patients with lesions of the cervix in this institution has

62. Döderlein, G.: Zentralbl. f. Gynäk. **55**:968, 1931.

63. Lacassagne, A.: Strahlentherapie (supp.) **13**:156, 1930.

64. Warren, Shields: The Grading of Carcinoma of the Cervix Uteri as Checked at Autopsy, Arch. Path. **12**:783 (Nov.) 1931.

been calculated. If the diagram (fig. 15) is used, point 15, which represents a distance of 5 cm. from the lower capsule of the cervix, receives approximately 335 per cent skin erythema dose. Point 2, 1 cm. distant from the capsule, receives 5,600 per cent skin erythema dose, other regions receiving doses intermediate between these extremes. This represents the entire radiation from all sources received in the primary treatment and not that from the capsules alone. The first thing apparent is the enormous diminution in the quantity of radiation at a point a few centimeters away from the largest source. The portions of the tumor near the radiating capsules are overdosed. A few centimeters farther

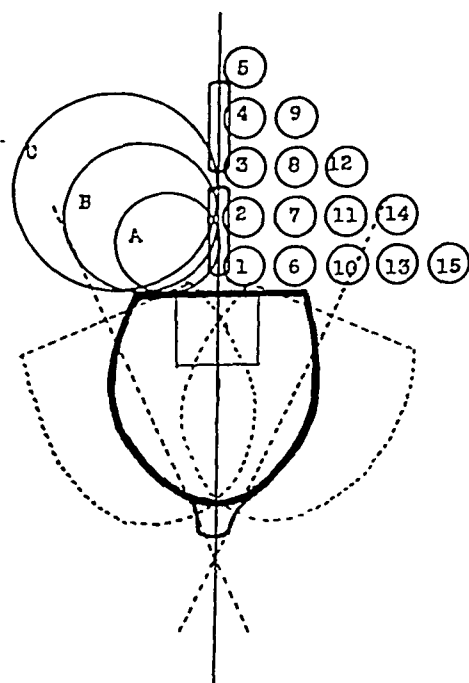


Fig. 15.—Cervix tandem and bomb in position. The distribution of points is discussed in the table on dosage.

out the dose becomes less than sufficient to cure most epidermoid carcinomas similar in type to the cervix group but occurring in other locations.

All of the epidermoid carcinomas of the cervix receive the same treatment so far as it is possible to administer it. They all are subjected to doses which are of caustic intensity at the nearest portion of the tumor and which are too feeble greatly to affect a tumor lying in a radius of beyond 5 cm. This fact makes me believe that it is difficult to estimate radiosensitivity by the percentage of local cures. To do this satisfactorily would seem to require a much more homogeneous irradiation of the field. When recurrence is noted, it is essentially impos-

sible to state from whence it proceeds. Is it really a local recurrence, does it spread backward from a point in the lightly irradiated periphery or does it extend down from the uterine body? In other words, it is not known how much radiation the point from which the recurrence proceeds received in the initial treatment. Were the doses lower and more homogeneous, much more information might be obtained. That is really the way they were obtained in other locations, and a sort of average limen of sensitivity was established.

Speed of regression following treatment might be expected to furnish some estimate of radiosensitivity. However, there is little satisfaction in clinical examination of the cervix during an acute reaction to radium.

I believe that there is a definite discrepancy between the grading of cancer of the cervix by Döderlein and by the staff of the Memorial

*Dosages at Various Points in Figure 15*

Point	Dose (% Skin Erythema Dose)	Point	Dose (% Skin Erythema Dose)
1.....	2,060	9.....	870
2.....	5,690	10.....	735
3.....	1,510	11.....	715
4.....	3,585	12.....	610
5.....	590	13.....	495
6.....	1,035	14.....	485
7.....	1,205	15.....	335
8.....	970		

Hospital. We differ considerably from Döderlein as to what constitutes an undifferentiated carcinoma. The grade III anaplastic carcinomas considered highly radiosensitive by Healy and Cutler are far different from the solid unripe carcinomas of Döderlein as judged by his excellent colored illustration. It seems to me that Döderlein's pictured unripe, solid carcinoma is an infected, degenerating, rather adult, squamous type and not at all similar to what we consider the highly radiosensitive variety. Furthermore, there are marked discrepancies in the relative numbers of different types of cervical epidermoid carcinomas in Döderlein's material and in ours. Döderlein found that the majority of his tumors belong in the unripe group. In the material from the Memorial Hospital, which averages about 175 new cases per year, I find not more than from 10 to 12 per cent in the anaplastic radiosensitive group. It is obvious that such large discrepancies must lie in the method of grading. Healy and Cutler's conclusions cannot, therefore, be compared with Döderlein's. As to statements that cure is a function of radiosensitivity, I know of little to justify them. Cure

is a far more complicated matter in cancer of the cervix. I believe that there are differences in the sensitivity of cancer of the cervix; that the cellular, disorganized, anaplastic varieties resembling solid diffuse transitional cell carcinoma are highly radiosensitive; that there are essentially no differences between the fully adult and the slightly less adult plexiform types of Healy and Cutler, and that there is little if any relation between sensitivity and cure with the methods generally employed in the treatment of epidermoid carcinoma of the cervix. Only time will tell.

#### CORPUS CARCINOMA

Whereas a considerable literature exists on the relation of structure to radiosensitivity in carcinoma of the cervix, there is little available on corpus carcinoma. There are numerous statistics of curability of corpus carcinoma by radium, but practically none on radiosensitivity. It has long been known that there are marked differences in the prognosis of different types of corpus cancer. Mahle,<sup>65</sup> for instance, found no deaths from grade I adenoma malignum and no survivals after surgical intervention for grade IV, completely undifferentiated carcinomas. Lindsay<sup>66</sup> confirmed these results and found that embryonal carcinoma (diffuse carcinoma, grade IV) yields better to irradiation than to surgical intervention.

It is not my purpose to discuss the comparative value of surgical intervention and irradiation in the treatment of corpus carcinoma, but merely to ascertain the prevailing opinion on the relation of structure to sensitivity. The only work dealing especially with these matters is that of Healy and Cutler.<sup>67</sup> These authors have divided their corpus carcinomas, with the exception of adeno-acanthoma and adenomyocarcinoma, into four groups. Group I consists in the papillary malignant adenomas. This is a characteristic form in which the growth is superficial and entirely papillary (fig. 16). The papillae are low, the cells are not atypical, and there is no infiltration. Some cases are difficult to distinguish from adenomatoid endometritis. Cures have followed curettage alone. Group II comprises cases in which the uterine glands are markedly elongated and enlarged. They are thrown into folds and convolutions to form papillae. The cells are cuboidal or cylindric and are arranged in compact layers about the gland lumen (fig. 17). The nuclei are hyperchromatic. Mitoses are often abundant. The stroma is scanty, and adjacent glands come in direct contact. Polarity of the cells is everywhere maintained. Group III, adenocarcinoma, includes all cases in which the tumor forms solid masses of cells (fig. 18) which grow in cords or columns. There is definite loss of cell polarity. The

65. Mahle, A. E.: *Surg., Gynec. & Obst.* **36**:385, 1923.

66. Lindsay, W. S.: *Surg., Gynec. & Obst.* **44**:646, 1927.

67. Healy, W. P., and Cutler, Max: *Am. J. Obst. & Gynec.* **19**:457, 1930.

cells are more atypical. Not infrequently portions of the tumor show adenoma malignum and others show adenocarcinoma. In such circumstances the tumor is classed as adenocarcinoma. The glandular arrangement is maintained though more diffuse, solid and atypical. In group IV, diffuse (embryonal or anaplastic) carcinoma, cell polarity is completely lost. Glandular arrangement is absent. The growth is diffuse

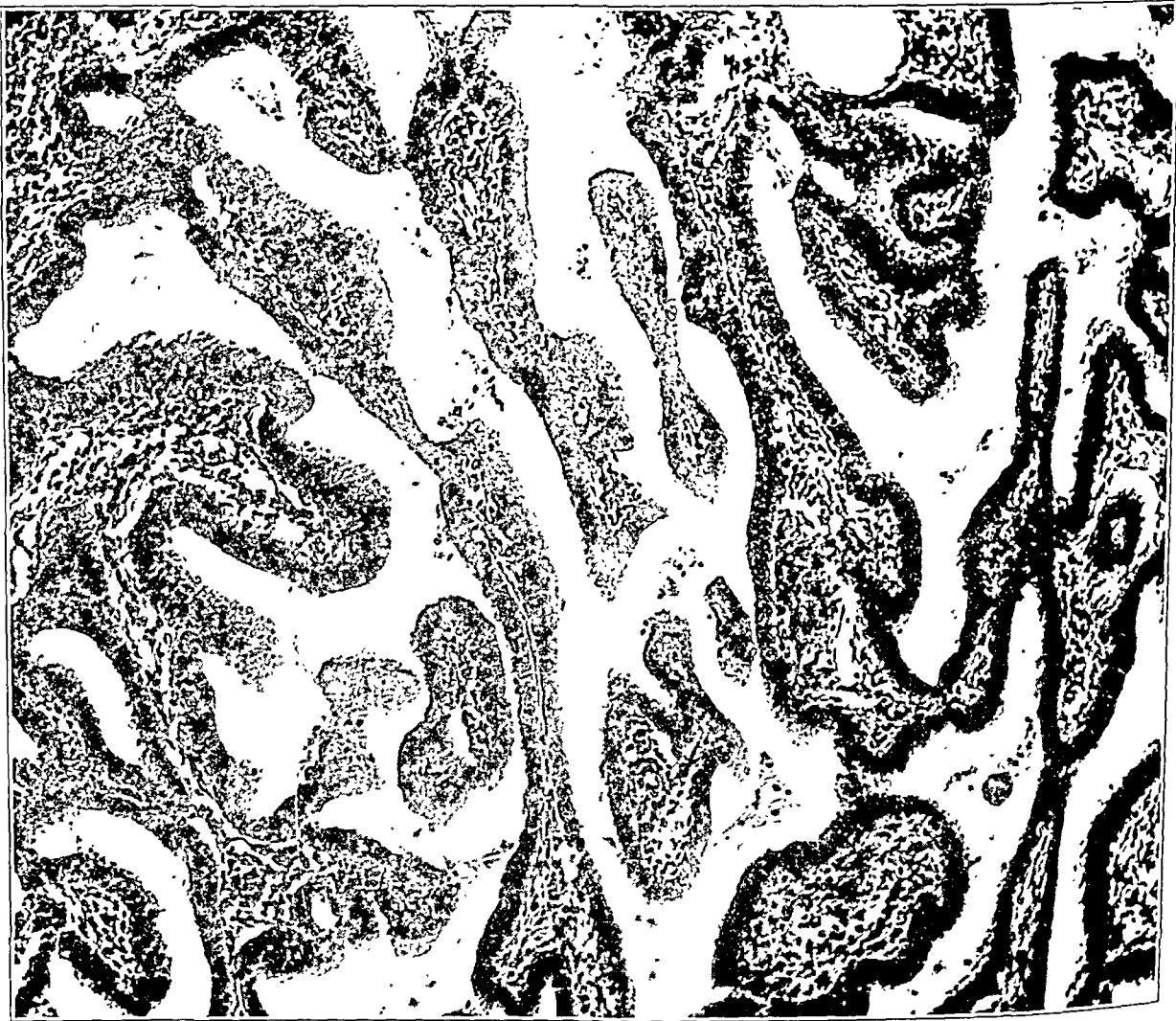


Fig. 16.—Corpus uteri; papillary adenoma malignum, grade I. Not per se sensitive, but usually superficial and within range of more caustic action of radium.

(fig. 20) and is composed of small round and polyhedral cells, closely packed, growing in sheets and cords. Nuclei are small and hyperchromatic, and the cytoplasm is scanty. There are marked signs of anaplasia. There is complete loss of differentiation. Mitoses are abundant and often atypical. The tumor may be difficult to distinguish from the anaplastic epidermoid carcinomas of the cervix so great is the

loss of differentiation. This variety of tumor was found in 12 per cent of the cases of Healy and Cutler. They reported 2 cases of unusual interest in demonstrating the high sensitivity of grade IV anaplastic carcinoma. In one, following a single low voltage cycle to the pelvis (exact dose not specified), the uterus showed rapid diminution in size, and hysterectomy three weeks later revealed massive necrosis of the

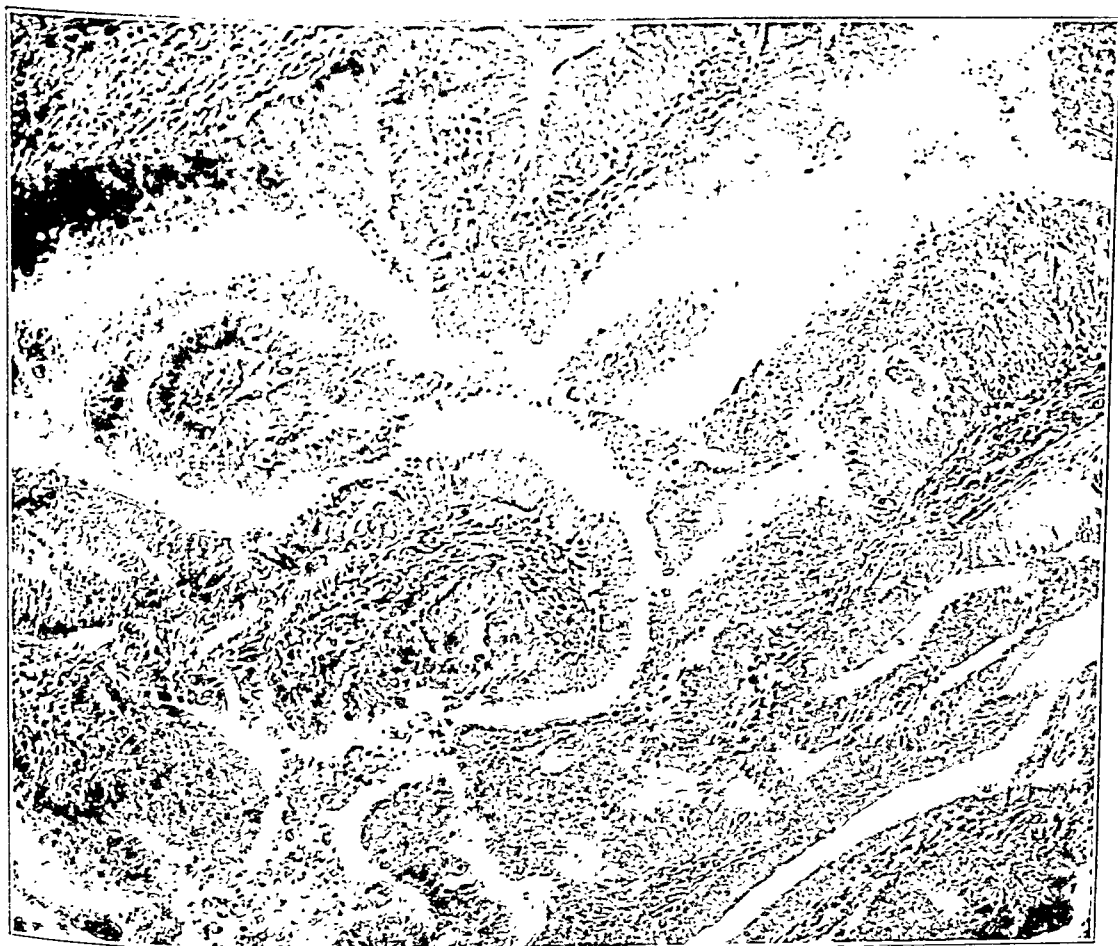


Fig. 17.—Corpus uteri; adenoma malignum, grade II. Not sensitive, but often curable, nevertheless, if within range of applicator.

tumor with but shadow cells remaining. Another patient with an advanced lesion and a uterus which extended 8 cm. above the symphysis remained well five years after moderate irradiation. After five years she underwent hysterectomy for suspected pyometra, since which operation she had remained well (six years). That this last patient was only clinically cured for the eleven year period and not pathologically cured is unfortunately attested by the fact that about two years after the



appearance of Healy and Cutler's paper, she returned to the hospital with a massive peritoneal recurrence. This recurrence showed the same structure as the original uterine lesion. Apparently irradiation had caused restraint of growth over a number of years.

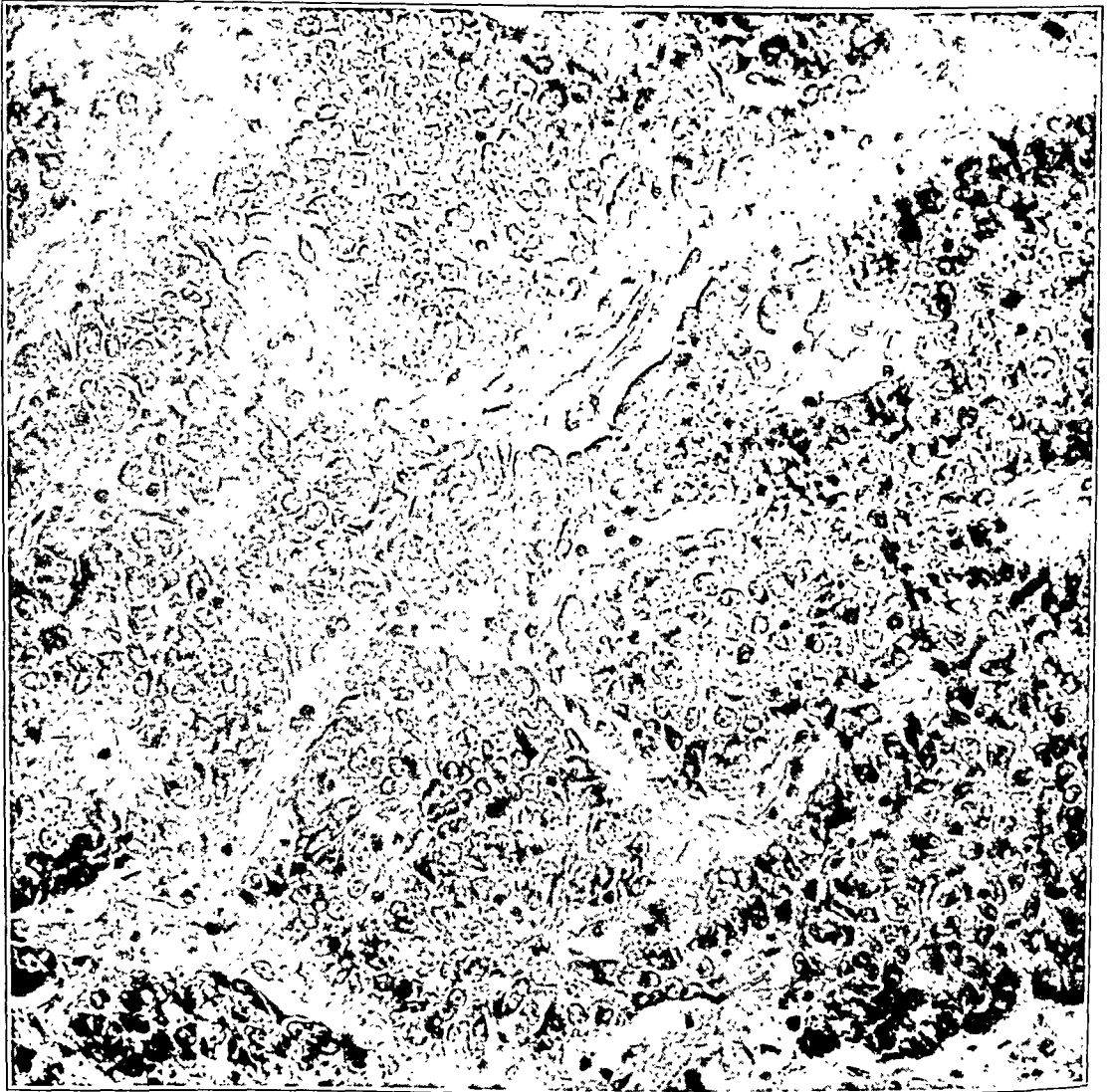


Fig. 18.—Corpus uteri; adenocarcinoma, grade III, slightly sensitive. The disease is apt to be advanced. The results after either surgical intervention or treatment with radium are apt to be bad.

Healy and Cutler regarded adeno-acanthoma (fig. 19) as radio-resistant. They stated that as a whole corpus carcinomas are but slightly sensitive, with the exception of the anaplastic group. The curability of the lower grades of corpus cancer is less dependent on sensitivity than it is on the superficial character and accessibility to large

amounts of intra-uterine radium. The ideas pertaining to the resistance of the average corpus carcinoma are held not only at the Memorial Hospital, but at the Radium Institute of Paris (Regaud<sup>22</sup>). It should again be emphasized that the radioresistance of these tumors does not mean that many cannot be cured by radium. Cures are dependent on

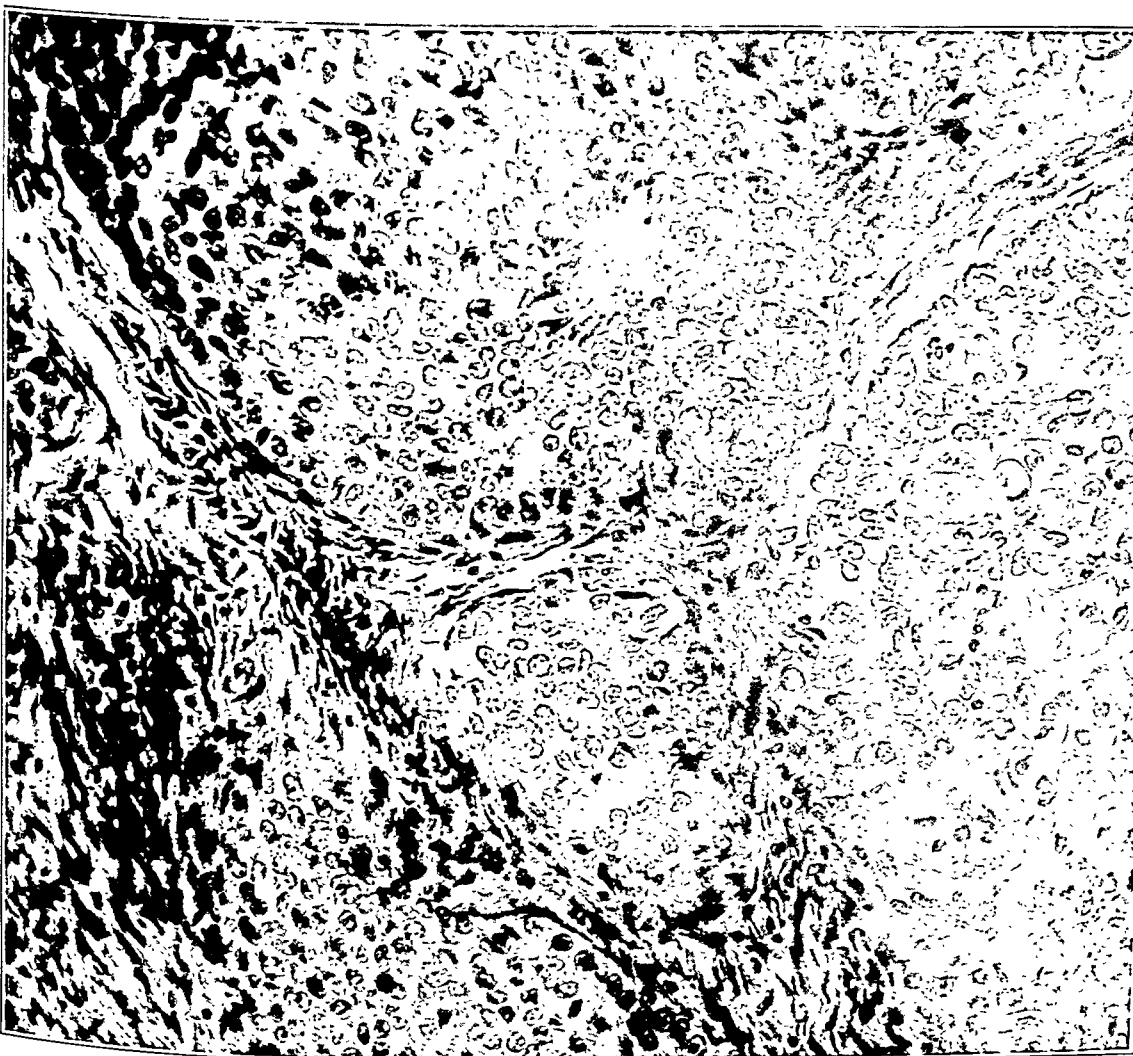


Fig. 19.—Adeno-acanthoma of corpus uteri; radioresistant.

many things other than sensitivity, and a discussion of curability is foreign to the purpose of the present paper.

#### CARCINOMA OF THE VAGINA AND OF THE VULVA

These tumors are similar in structure to the epidermoid carcinomas of the cervix. The impression one gains from the radiologic literature

retarded. The patient is living after nearly four years, but the disease has not disappeared, and is now showing activity.

#### CHORIONEPITHELIOMA

Schmitz and Hueper<sup>73</sup> reported favorable results in the radiation treatment of chorionepithelioma. Wintz<sup>74</sup> stated that chorionepitheliomas are much more sensitive than the normal uterine tissues and considerably more sensitive than the usual uterine carcinomas. Fortunate is the clinician who can gather a sufficient number of choriocarcinomas to make reasonably certain of their radiosensitivity. Symmers (Gordon<sup>75</sup>) found 1 probable choriocarcinoma among 35,000 surgical specimens and during 8,000 autopsies at Bellevue Hospital. The number might be expected to be proportionately larger in a special hospital for patients with cancer. Yet I can recall but 3 among the last 20,000 specimens. The author who believes that he has obtained cures in any considerable number of cases of choriocarcinomas by any means must first triply assure himself that what the pathologist has called choriocarcinoma is not chorio-adenoma destruens, syncytial endometritis, syncytioma or even early normal gestation. The diagnosis of choriocarcinoma presents many difficulties and must be made with caution. Although possibly not pertinent to uterine choriocarcinoma, I have observed relative radioresistance in embryonal carcinoma of the testis when choriocarcinomatous structures were present. There is much in the structure and origin of choriocarcinoma which would lead one to believe that it is radiosensitive, but no confirmatory body of proof in sufficient quantity is as yet available. In a recent paper Eymer<sup>76</sup> expressed doubt that all choriocarcinomas possess a high radiosensitivity.

#### MALIGNANT TUMORS OF THE OVARY

The ovary is a complex organ. Malignant tumors of the ovary are widely different histogenetically. Moreover, the histologic origin of certain ovarian tumors is by no means clearly understood. Much less is known concerning the correlation between tumor type and radiosensitivity in ovarian tumors than, for example, in carcinoma of the cervix, in which the histogenesis is relatively simple.

The diffuse embryonal carcinomas of the ovary (embryonal carcinoma with lymphoid stroma; seminoma ovarii) parallel in general similar tumors of the testis in their response to radiation. They are radiosensitive, often highly so. The reader is referred especially to the

73. Schmitz, Henry, and Hueper, Wilhelm: *Malignant Chorionepithelioma Uteri*, J. A. M. A. **95**:1413 (Nov. 8) 1930.

74. Wintz, H.: *München. med. Wchnschr.* **78**:781, 1931.

75. Gordon, O. A., Jr.: *Surg., Gynec. & Obst.* **36**:242, 1923.

76. Eymer, H.: *Strahlentherapie* **44**:241, 1932.

work of Jean Hoche.<sup>77</sup> Hoche discussed the similar responses to radiation shown by "seminomas" of the testis and ovary. He reported but a single case and seemed to assume that these diffuse embryonal tumors of the ovary will behave much like the corresponding testicular group. At the Memorial Hospital it must be admitted that the same degree of success in controlling "seminoma" of the testis and of the ovary has not been obtained. The few cases of this tumor of the ovary which have been seen have not been successfully controlled. Massive regression may be expected, but massive recurrence with gradually increasing resistance has occurred. It may be well to explain that we do not recognize in "seminoma" a tumor of adult origin as do Chevassu and many others, but prefer to regard it as a form of embryonal diffuse carcinoma. Furthermore, we have difficulty in separating this type from diffuse granulosa cell tumors. I have no good explanation for our observation on the lesser success in controlling these ovarian tumors. It is possible that were an equal series of cases of tumors of the testis and of the ovary available, no essential differences would be apparent.

Granulosa cell tumors (fig. 21) are usually benign. Occasionally they may be malignant. Malignant granulosa cell carcinoma is radio-sensitive. The initial regression may be marked. Clinically, complete regression or decided partial regressions in the cases at the Memorial Hospital have been followed by fairly prompt recurrence and death. The radiation administered was all the patient could tolerate, and the result cannot be assigned to inadequate therapy.

The papillary cystic adenocarcinomas of the ovary are apt to exhibit wide differences in histologic structure. Different regions of the same tumor may show different structures, ranging from the adenomatous to the solid. Solid masses are intermingled with intracystic papillary adenomatous areas. The tumors are often mucinous. It is not surprising that they show no particular degree of radio-sensitivity. When these tumors form diffuse implantation metastases, opinions are conflicting as to whether or not they are sufficiently sensitive to permit retardation of growth after irradiation. Taylor<sup>78</sup> saw no influence of radiation. Heyman,<sup>79</sup> Ford<sup>80</sup> and Strassman<sup>81</sup> were more enthusiastic. At the Memorial Hospital experience has shown that the lower grades of papillary ovarian carcinoma yield the better results to irradiation. Of inoperable disease in which implantation has occurred, only the low grade papillary adenoma malignum with psammoma bodies has yielded marked anatomic regressions and

77. Hoche, Jean: Bull. Assoc. franç. p. l'étude du cancer **19**:476, 1930.

78. Taylor, H. C., Jr.: Am. J. Cancer **15**:2517, 1931.

79. Heyman, J.: Strahlentherapie **37**:254, 1930.

80. Ford, F. A.: Am. J. Obst. & Gynec. **16**:1, 1928.

81. Strassman, in discussion on Schäfer: Zentralbl. f. Gynäk. **46**:514, 1922.

possible cures. One young patient with a more malignant papillary adenocarcinoma metastatic to a superficial region—the inguinal nodes—experienced a marked regression. In many patients with peritoneal metastases the rate of accumulation of fluid has been retarded. Inoperable masses are occasionally sufficiently sensitive to become operable after radiation. Healy<sup>82</sup> stated that when the tumors are sufficiently aggressive to have invaded retroperitoneal nodes, the pallia-

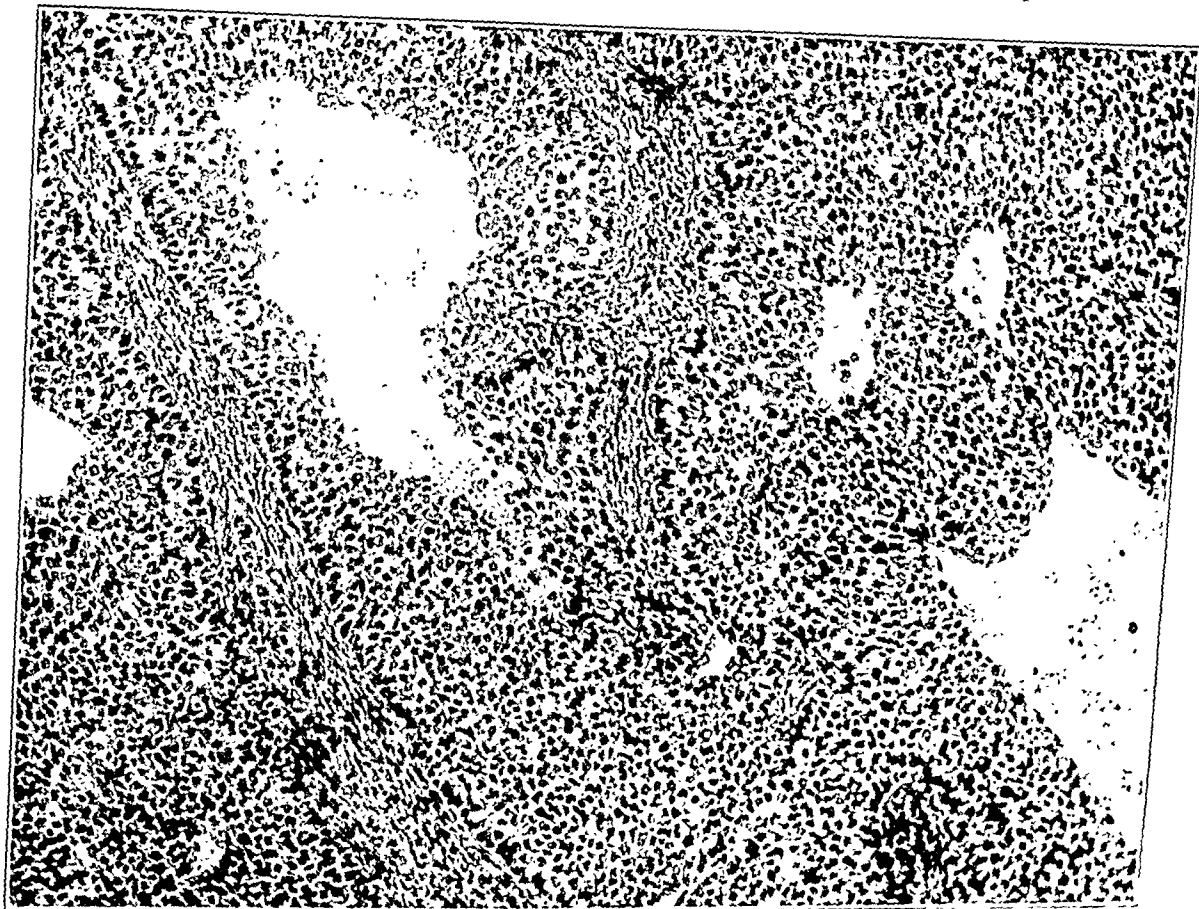


Fig. 21.—Ovary; relatively sensitive granulosa cell carcinoma. Apt to recur and to show progressive increase in resistance.

tion by irradiation is essentially nil. Patients whose lesions are producing intestinal obstruction have not been benefited by irradiation. No information is available on the behavior to irradiation of the large group of rare miscellaneous tumors of the ovary.

Two recent papers have appeared dealing wholly or partially with ovarian neoplasms. Wintz<sup>83</sup> reported that irradiation after incomplete

82. Healy: Personal communication to the author.

83. Wintz, Hermann: *Strahlentherapie* 44:201, 1932.

operation has yielded 40 per cent three year cures and 25 per cent five year cures. He did not separate the tumors into their various types, hence his study, like so many others, affords no information in the field of radiosensitivity. Wintz stated, however, that the radiosensitivity is not definitely ascertainable from the histologic structure. The "extraordinary radiosensitivity" of granulosa cell tumors even with metastases is emphasized by Borak<sup>84</sup> and the sensitivity of embryonal carcinoma (*Embryozytom*) by Nemenow.<sup>13</sup>

#### MALIGNANT TUMORS OF THE KIDNEY

The papillary and solid renal adenocarcinomas and the hypernephromas are quite radioresistant and do not encourage the idea of cure with radiation. Whether or not they are sufficiently sensitive in rare instances to permit of palliation by irradiation I am not prepared to state. Occasionally their diffuse anaplastic metastases have proved quite sensitive, although the primary tumor showed no change (figs. 22 and 23). Such sensitivity is of academic interest only. In discussing the response to radiation of pulmonary metastases of hypernephromas the observations of Bumpus<sup>85</sup> on the spontaneous disappearance of such lesions should not be forgotten. Papillary epidermoid carcinomas of the renal pelvis have not been appreciably influenced by the quantity of radiation reaching them from external sources. Data on their sensitivity are lacking.

The large group of embryonal tumors of the kidney offers more encouragement. These tumors show markedly varying structures. There is every stage from fairly well developed, adult-looking, tubular, renal carcinomas down to the diffuse embryonal adenomyosarcoma of Wilms. The degree of embryonal nature of these tumors is so varied that differences in the response to radiation must surely occur. Yet there are no observations which may be interpreted in a quantitative manner. Diffuse Wilms' tumors are often extremely radiosensitive. They exhibit regressions equaled only by lymphosarcomas, some thymomas, the embryonal carcinomas with lymphoid stroma of the testis, the neurocytomas of the retroperitoneal group, rare lympho-epitheliomas and the endothelial myelomas (Ewing's tumors) of bone.

While the Wilms tumors show extraordinary regression under external irradiation, recurrence is almost inevitable. Once recurrent, an acquired radioresistance seems to develop, making each successive regression less and less. Furthermore, fibrosis and adhesions develop, tying down the adjacent abdominal viscera to the tumor and rendering surgical intervention impossible. This has led to the assumption that

84. Borak, J.: *Strahlentherapie* **44**:601, 1932.

85. Bumpus, H. C., Jr.: *J. Urol.* **20**:185, 1928.

if surgical intervention is to be done, it should follow the maximum initial irradiation regression. Barringer,<sup>86</sup> in discussing these tumors, stated that their radiosensitivity diminishes with the increasing age of the patient. This may be so, yet had Barringer's cases been studied from the point of view of tumor structure, the influence of age might have had a different interpretation. The Wilms tumor is fortunately not common. The records of the Memorial Hospital report 16 such tumors. Of the 16 patients, 13 are dead, and the other 3 have been lost from observation. They are undoubtedly dead. Quite obviously,



Fig. 22.—Renal carcinoma; long-standing tumor; calcified in places and necessitated cutting with saw; radioresistant.

unless radiation is to occupy a purely palliative rôle with these tumors, it must be decidedly improved. In many of the cases in the Memorial Hospital the irradiation was inadequate.

It is most curious that these sensitive tumors disappear with such dramatic rapidity and yet recur so regularly. If explanation is sought, it may possibly be found in certain of their gross peculiarities. First, the tumors are very large. Second, they tend to infarction readily.

<sup>86</sup> Barringer, B. S., in discussion on Dean, A. L., Jr., and Pack, G. T. Embryonal Adenosarcoma of the Kidney, *J. A. M. A.* **98**:10 (Jan. 2) 1932.

When infarction exists, one finds, microscopically, islands of living tumor cells in masses of caseous or liquefied material. Such cells may show little evidence of damage by radiation. Is it not possible that the recurrence is due to persistence of viable cells in wide necrotic areas where there is little opportunity for the development of rapid fibrosis? Persistent cells in the vicinity of well developed capsular vessels may likewise account for recurrences.

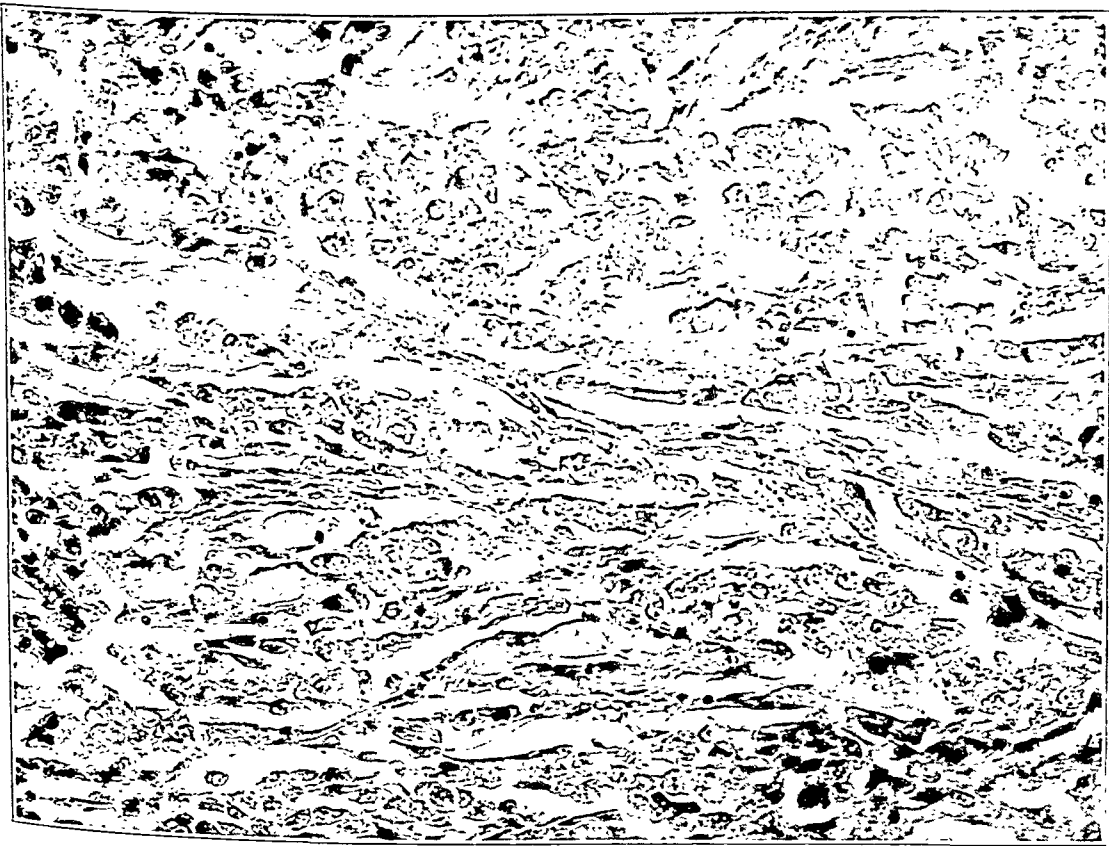


Fig. 23.—The same tumor as in figure 22 invaded the renal vein and produced anaplastic, relatively sensitive metastases in bizarre locations, including the tongue and cardiac muscle. Photograph from myocardium.

#### CARCINOMA OF THE SUPRARENAL GLANDS

Medullary carcinomas of the suprarenal glands are usually widely metastasizing neoplasms. Nothing is known about their radio-sensitivity. Small cell neurocytomas of the suprarenal glands are exceedingly sensitive, thus behaving quite contrary to the group of neurogenic tumors as a whole, quite obviously because they are histogenetically quite different.



## TERATOMA OF A TESTIS

Adult carcinomas are rarely found in the testis. In stating this fact, I admit that I do not consider the so-called seminoma (fig. 24) as an adult tumor. Adult carcinoma is so rare that observations on its sensitivity are lacking. There is much information on the behavior of embryonal carcinomas of the testis, although all of the data so far are based on skin doses or even applicator doses, and none on tumor



Fig. 24.—Testis; solid embryonal carcinoma; Chevassu's seminoma; radiosensitive.

doses. The prediction of radiosensitivity in embryonal carcinomas of the testis is based both on histology and on anatomy. There are marked differences in type. Adult teratomas are resistant, although when they contain more diffuse, embryonal areas, they may regress without altering the clinical aspect of the testis, since the presence of residual adult bone, cartilage, mesenchyme, etc., renders the mass pseudoresistant. Squamous carcinoma may develop in cases of com-

plex teratoma. This tumor is resistant. We have observed 1 embryonal tumor of the groin made up largely of adult-looking glia tissue. This tumor was resistant. In discussing embryonal tumors of the testis and, for that matter, elsewhere, it must be remembered that although the tumors are of embryonal origin, many rapidly attain an adult structure. The bone, for example, of complex teratoma is fundamentally a con-

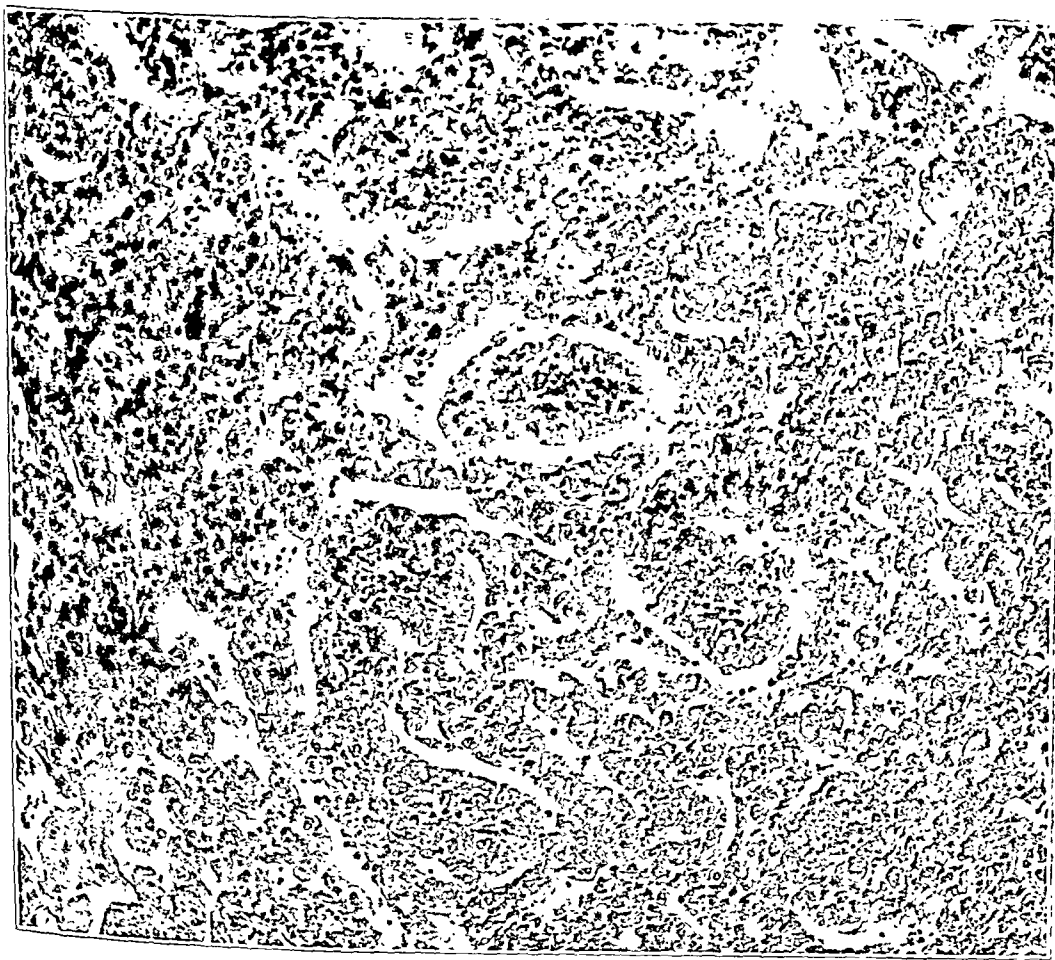


Fig. 25.—Testis; more radioresistant embryonal adenocarcinoma.

stituent of an embryonal tumor, yet it may have attained a structure indistinguishable from adult bone. Similar statements apply to other tumors outside the testicular group. Among the embryonal renal tumors there is every gradation between tumors of diffuse embryonal structure and those with relatively adult nephrogenic tissue, although all of the tumors are of embryonal origin.

Embryonal adenoma malignum or adenocarcinoma (fig. 25) makes up the structure of many testicular embryomas. The latter of these

(adenocarcinoma) is highly malignant and only moderately sensitive to any dose deliverable to the tumor. This tumor produces, next to choriocarcinoma, the most hopeless of the testicular metastases. Embryonal carcinoma with lymphoid stroma (fig. 26) is a highly sensitive tumor. Both the primary tumor and the metastases are sterilizable by massive doses. We have a patient who has been free from disease for more than six years, in whom not only extensive abdominal metastases but also pulmonary and supraclavicular metastases were present. It is unlikely that irradiation will duplicate this result frequently. Nevertheless,

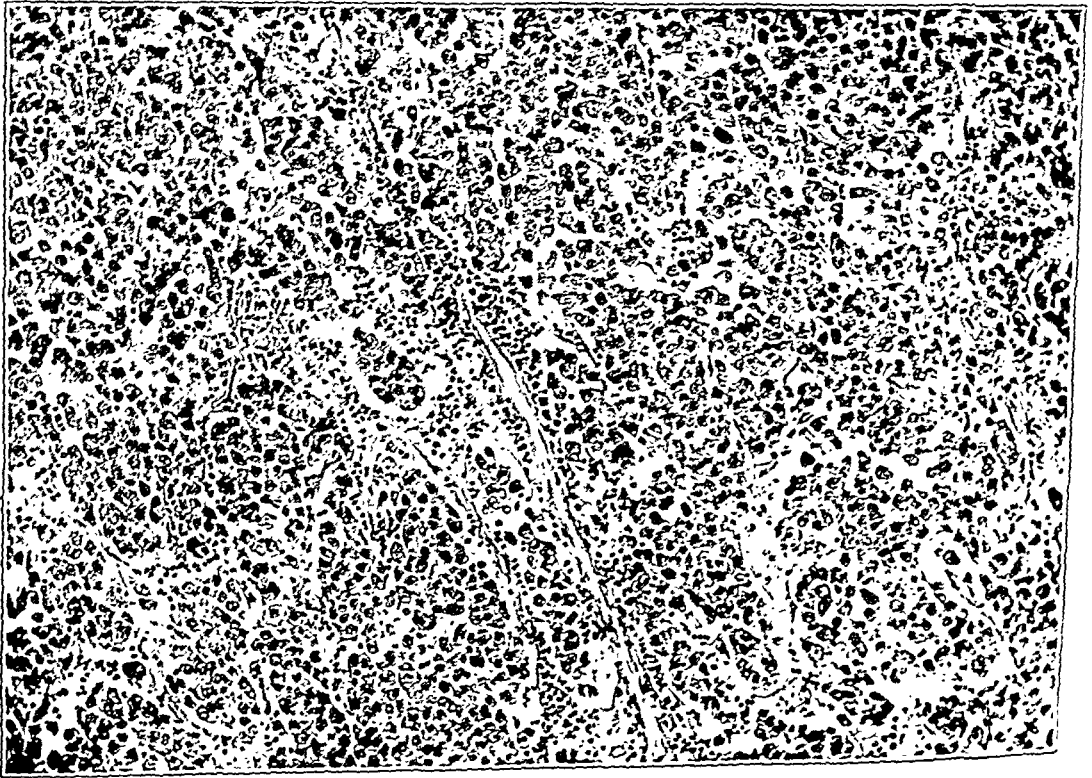


Fig. 26.—Testis; radiosensitive embryonal carcinoma with lymphoid stroma.

Barringer, Stewart and Spies<sup>87</sup> were able to report 24 (30 per cent) of 81 patients with inoperable local recurrences and metastases free from disease for from one to ten years. Radiation has entirely altered the prognosis of testicular teratoma, but the radiation must be far from homeopathic as to dosage. The first patient with teratoma of the testis who was treated at the Memorial Hospital more than a decade ago has just returned for excision of a benign radium ulcer of the abdominal skin, but is free from disease. Others already have cutaneous atrophy

87. Barringer, B. S.; Stewart, F. W., and Spies, J. W.: *Ann. Surg.* **91**:115, 1930.

and telangiectases, but are well more than five years after treatment for one of the most malignant tumors in the whole category of neoplastic diseases.

It is our general impression that the metastases of embryonal carcinomas of the testis are apt to be more radiosensitive than the primary lesions. Furthermore, primary tumors of the same histologic type show considerable variations in the degree of destruction by radiation. Small tumors tend to vanish more completely than larger ones. Their destruction may be so complete that the pathologist unfamiliar with pathologic changes caused by irradiation may make an erroneous diagnosis of gumma. This error has been made in our laboratory. In the larger tumors the local destruction with the doses utilized is often incomplete. There is often a narrow zone of viable tumor at the periphery of the excised mass. This zone emphasizes the importance of circulatory changes and infarction in the production of destruction by irradiation. The tumor nearest the normal testicular tissue is probably best nourished and consequently is more apt to resist destruction. When tumors occupy most of the testis and distend the tunic, rupturing it at one or more points, it may be noted that the portion outside the tunic remains viable, while that inside is necrotic. This may depend on the strangling effect of irradiation edema on cells within a tense tunic.

Attention should be called to the spurious radioresistance of embryonal carcinomas of the testis in some instances. Irradiation may convert an active tumor mass into a necrotic hematoma which, of course, fails to diminish in size and which gives the impression that one is dealing with a resistant tumor. This has occurred especially in chorioma of the testis, but also in other types. Chorioma of the testis in itself is relatively resistant. Its metastases have given poor reaction to radiation.

#### CARCINOMA OF THE URINARY BLADDER

There is no available information on the relation of structure to the irradiation behavior of carcinomas of the bladder. I believe it impossible to determine this matter from the material at the Memorial Hospital, since the doses used in cancer of the bladder are extremely large (Dean and Quimby<sup>88</sup>). The superficial tumors are largely removed by electrosurgery, and only the base is implanted with radium. The clinically determinable area of infiltration is heavily treated. The extent of pathologic infiltration cannot be accurately estimated. If the lesion recurs after irradiation, it is difficult to say which dose in the original treatment reached the area from whence the recurrence arose. It is often impossible to say whether the patient has a recurrence or a new

88. Dean, A. L., Jr., and Quimby, E. H.: Surg., Gynec. & Obst. **53**:89, 1931.

lesion. Much more information should be obtainable from the results of high voltage roentgenotherapy alone. Barringer<sup>89</sup> expressed the belief that doses which can be delivered by external means often even fail to control hemorrhage. He consequently placed so little emphasis on external radiotherapy that his material is little calculated to yield data on sensitivity.

The results of Pfahler<sup>90</sup> are so disappointing that they afford little to encourage one in the belief that any decided number of tumors of the bladder are radiosensitive. Burnam and Neil<sup>91</sup> seem insufficiently impressed by any degree of sensitivity in their tumors of the bladder to place much importance on external irradiation in their therapeutic schema. Schmitz and Laibe<sup>92</sup> reported excellent results with roentgenotherapy and discussed the relation between histology and the clinical result, yet, unfortunately for my purpose, they discussed it in terms of generalities and not in regard to the tumors they were treating. Gunsett<sup>93</sup> described good therapeutic results with roentgenotherapy, but failed to discuss them in terms of tumor structure. The question of the relation between structure and sensitivity of cancers of the bladder must await further analysis. It must await a structural analysis of tumors treated by noncaustic dose of roentgen rays.

#### CARCINOMA OF THE PROSTATE

Ferguson<sup>94</sup> has recently reviewed the literature on the irradiation of prostatic cancer, and he made a decidedly worth while addition. It is obvious that the irradiation of prostatic cancer has not been pursued in any manner calculated to deliver a reasonable dose to a radioresistant glandular carcinoma. Reports on the restraint of prostatic cancer by radiation have not adequately considered the wide difference in the clinical manifestations and varying duration of different types of prostatic cancer. Ferguson saw essentially no histologic changes in tumors which had received less than 80 per cent skin erythema dose. Doses in excess of this amount, but less than 150 per cent skin erythema dose, produced changes in some instances but not in all. The main effects were fibrosis, arteritis and hyaline degeneration. Transient hydropic changes in the tumor cells occurred. Over 150 per cent skin erythema dose caused changes in all cases. Fibrosis was marked. Infiltrating

89. Barringer: Personal communication to the author.

90. Pfahler, G. E.: Surg., Gynec. & Obst. **53**:680, 1931.

91. Burnam, C. F., and Neil, William, Jr.: Am. J. Roentgenol. **16**:219, 1926.

92. Schmitz, Henry, and Laibe, J. E. F.: Roentgen-Ray Treatment of Inoperable Carcinomas of the Urinary Bladder, J. A. M. A. **87**:1541 (Nov. 6) 1926.

93. Gunsett, A.: Acta radiol. **13**:1, 1932.

94. Ferguson, R. S.: Am. J. Cancer **16**:783, 1932.

cells seemed to undergo atrophy from pressure necrosis and capillary starvation. Hydropic swelling and fragmentation were observed in the larger clusters of cells. Marked alterations in the tumor, approaching sterility, were caused only by properly distributed interstitial irradiation. Ferguson believes that the total tissue dose should vary between 7 and 12 skin erythema doses. He reported 1 case only of sensitive prostatic cancer. Regression occurred in the primary mass and the metastasis of the lung, but not in the bone. Bumpus<sup>95</sup> found the duration of life in cases of prostatic cancer roughly proportional to the milligram hours of treatment with radium.

#### CARCINOMA OF THE THYROID

The literature contains many references to the use of radiation for malignant tumors of the thyroid. Tinker<sup>96</sup> stated that extensive operations appear unjustified when the favorable results of partial removal followed by radium are considered. Pemberton is of the opinion that "probably in no other malignant disease are radium and roentgen ray so valuable as in the treatment of malignant tumors of the thyroid." Lahey<sup>97</sup> has said that "when malignant degeneration of a thyroid adenoma is diagnosable, it is hopeless surgically. It is here that we have seen some of our very best results in a palliative way from x-ray treatment." Forssell<sup>98</sup> expressed the belief that next to cancer of the skin, lips and uterine cervix, cancer of the thyroid yields the most constant and valuable results with radiation. Schreiner<sup>99</sup> was less encouraged. Breitner and Just<sup>100</sup> reported favorable results in cases of "carcinoma," and unfavorable results in cases of "sarcoma." Haas<sup>101</sup> found carcinoma more sensitive than sarcoma. Clute and Smith<sup>102</sup> have the impression that radiation retards growth and delays the reappearance of malignant thyroid adenomas, but that it is of no value in "squamous cell," giant cell and small cell carcinoma. Portmann<sup>103</sup> reported moderate radiosensitivity in the "malignant adenomas," while

95. Bumpus, H. C., Jr.: *Am. J. Roentgenol.* **9**:269, 1922; *Surg., Gynec. & Obst.* **43**:150, 1926.

96. Tinker, M. B.: *The Diagnosis and Results of Surgical Treatment of Malignant Goiter*, *J. A. M. A.* **90**:508 (Feb. 18) 1928.

97. Lahey, F. H.: *Radiology* **6**:368, 1926.

98. Forssell, G.: *Am. J. Roentgenol.* **12**:301, 1924; *Brit. J. Radiol.* **3**:198, 1930.

99. Schreiner, B. F.: *Acta radiol.* **7**:419, 1926.

100. Breitner, B., and Just, E.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **38**:262, 1924.

101. Haas, W.: *München. med. Wchnschr.* **74**:1734, 1927.

102. Clute, H. M., and Smith, L. W.: *Cancer of the Thyroid Gland*, *Arch. Surg.* **18**:1 (Jan.) 1929.

103. Portmann, U. V.: *Strahlentherapie* **31**:102, 1929.

papillary carcinomas, scirrhus carcinomas and carcinosarcomas are resistant. Berven<sup>104</sup> reported 15 per cent of 39 patients with "malignant goiter" well for five years. The majority had inoperable tumors.

Throughout these papers there is no sufficient information as to the exact relation between the structure of the tumor and the response to radiation. For example, Portmann found that there is a certain degree of sensitivity in "malignant adenoma," yet in reviewing his papers I cannot find that the term malignant adenoma applies to any given histologic type of tumor. He stated that "what we designate as malignant adenoma is a type of carcinoma of the thyroid gland which in 90 per cent of the cases can be proved to have originated in a pre-existing adenoma." This statement is further elaborated in the following quotation:

Rarely is the tumor made up of only one type of neoplastic cell. There are usually areas in which the morphologic characteristics of fetal adenoma are mixed with others which show the characteristic structure of adenocarcinoma, medullary, scirrhus, papilliferous or spindle cell carcinoma or a carcinoma resembling sarcoma, or any combination of these.

Haagensen<sup>105</sup> has presented the best structural analysis of tumors of the thyroid in relation to their sensitivity. His paper is accompanied by illustrations sufficient to clarify the terminology applied to the tumors. He found the small cell carcinomas radioresistant. The large spindle cell and giant cell carcinomas, which many authors classify as carcinosarcomas, are resistant. Haagensen found that of 9 papillary cystadenocarcinomas (fig. 27), 5 showed no regression, 2 regressed completely, 1 regressed partially, and in 1 instance in which the primary tumor had failed to regress a postoperative recurrence disappeared completely after irradiation. Partial regression was noted in 1 Hurthle cell carcinoma metastatic to the lungs. Another similar tumor after slight regression remained stationary for five years. In 14 cases of adeno-

treated with about 15 skin erythema doses (30 millicurie hours in a 3 cm. mass) cannot well be compared with that of one which was treated, over a four months' period, with about 4 skin erythema doses, intermediate voltage, of which not more than 0.5 skin erythema dose could have reached the tumor depth at any one treatment. In many of the other tumor types there were large variations from one patient to the other—differences in anatomic setting and wide variations in the type



Fig. 27.—Thyroid; grade I papillary adenocarcinoma; little removed from hyperplasia. The patients are apt to be toxic. Relatively sensitive.

of radiation therapy, in quantity, source and time interval. There were great differences in the length of time the lesions had existed. Some patients suffered from advanced tracheal obstruction, although in a personal communication Portmann told me that he found this of little importance so far as the response to radiation is concerned. I believe that as yet there is no adequate series of carcinomas of the thyroid, treated with sufficient uniformity and by sufficient doses, to enable one to formulate a definite opinion on the sensitivity of these tumors. At



the Memorial Hospital I believe the doses, particularly in the older days, were too small. Portmann seems to have developed a fairly constant therapeutic method, yet the doses described by him are insufficient to cause the complete regression of even the oral tumors of moderate sensitivity, and I fail to see how one can expect to do much with fully aggressive glandular cancer by such means.

I fully agree with Haagensen that the best regressions are seen in the low grade papillary cystadenocarcinomas, and that in highly malig-

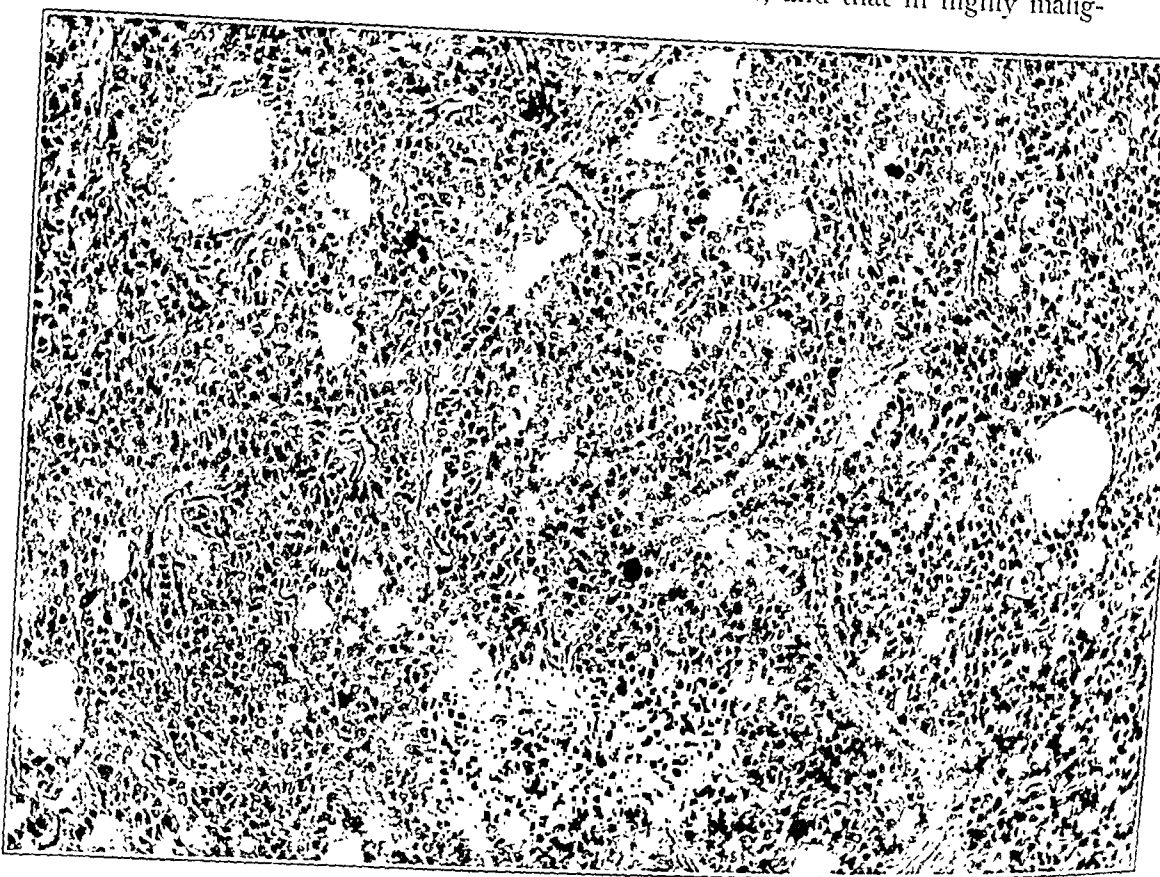


Fig. 28.—Thyroid; grade II adenocarcinoma. May be relatively sensitive, although not uniformly so.

nant solid or spindle cell cancer (fig. 29) regression may not be expected. It seems that many of these low grade papillary cystadenocarcinomas have not attained a full neoplastic autonomy. They may be of long duration. They exhibit periods of quiescence followed by exacerbation of growth. After excision their recurrences may be markedly delayed even though much tumor tissue remains. They often appear to be still under certain physiologic restraint. This fact may perhaps account for their relatively favorable response to radiation.

Even when in the lungs, irradiation of the primary thyroid mass may cause regression of the metastases to the lung, thus indicating a mechanism at least peculiar. Schaedel<sup>100</sup> described the regression of metastases to the lungs, bones and glands in 3 patients with struma maligna, after local irradiation of the thyroid.

Worthy of special mention are the small cell carcinomas (fig. 30) of the thyroid. They are described by Haagensen and by others as radioresistant. Within the past two years I have studied 4 cases of small round cell lesions of the thyroid. All of these were likewise

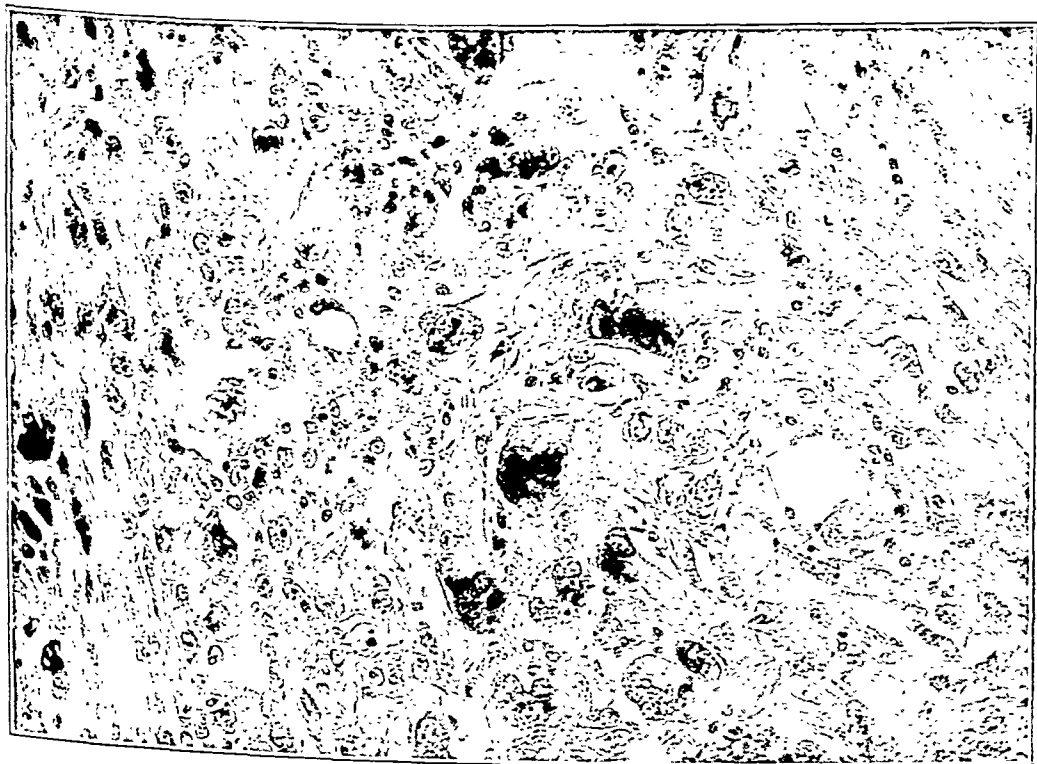


Fig. 29.—Thyroid; spindle and giant cell carcinoma; very radioresistant.

studied by Dr. Ewing. In all the question of their being small cell anaplastic carcinomas arose. When irradiated, they proved resistant. We do not know how to classify them, and, in fact, I believe that the diagnosis of small cell carcinoma of the thyroid is a difficult one. They are imperfectly separated from the Hashimoto type of Riedel's struma (struma lymphomatosa), and from lymphosarcoma. Portmann has found struma lymphomatosa radioresistant. The lesions we observed were not the usual type of lymphosarcomas as the disease exists elsewhere, since they did not involve nodes. Nor is there evidence that

<sup>100</sup> Schaedel, W.: München. med. Wchnschr. 69:1282, 1922.

they yielded the metastases that might be expected from carcinoma. All caused death by tracheal obstruction. The disease ran a rapid course and produced a bulky, soft, homogeneous, diffuse swelling of the thyroid, grossly suggestive of lymphosarcoma.

#### PRIMARY TUMORS OF THE BONE

The success of the x-rays in controlling benign giant cell tumors of the bone is well known. Just why giant cell tumors regress under

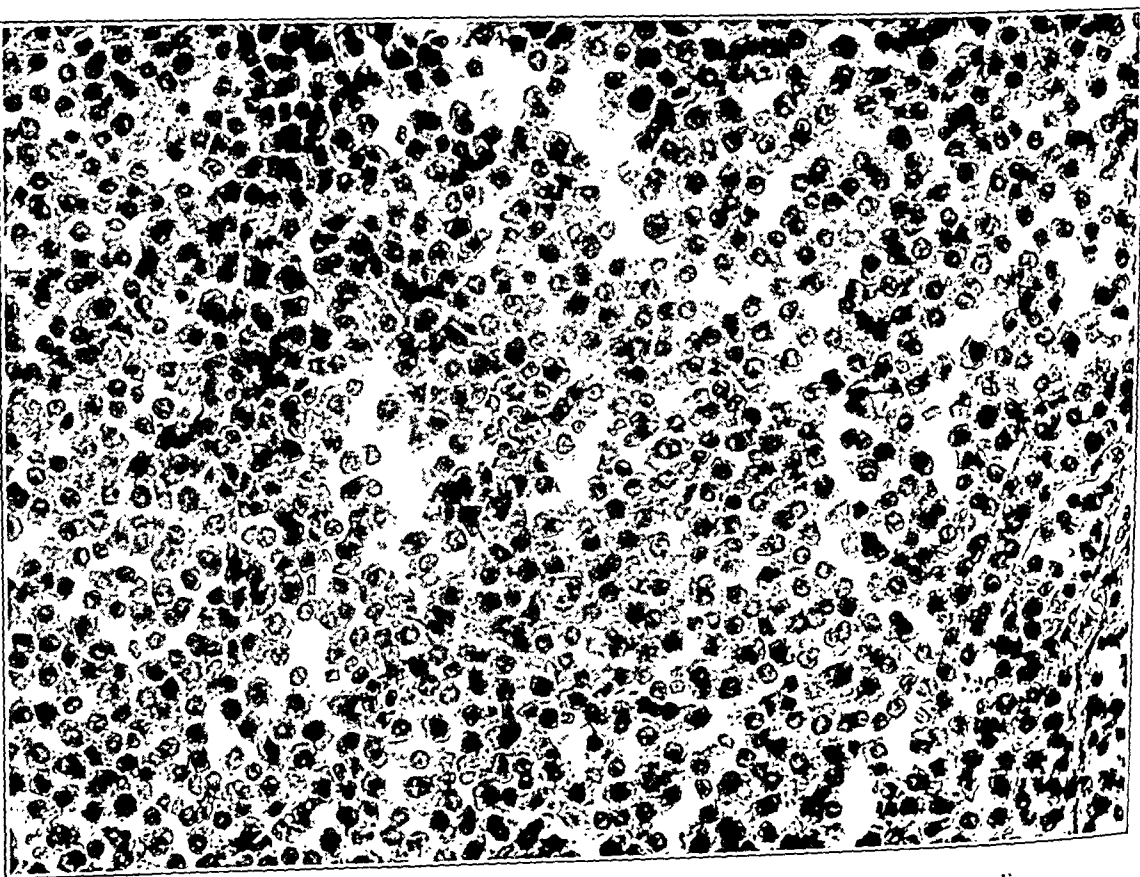


Fig. 30.—Thyroid; ? round cell carcinoma; ? struma lymphomatosa; radio-resistant.

radiation is not fully known. No opportunity is afforded to study them histologically during the healing period. The mechanism probably consists in decreasing vascularity, productive fibrosis and calcification. Sclerosis, once initiated, may progress of its own momentum without additional therapy. Successes are usually accomplished with moderate therapy, with doses repeated at long intervals, and massive doses may prejudice the result. Obviously, one cannot call giant cell tumors of bone radiosensitive in the usual sense of rapid destruction of tumor

cells; the process must be one of slow sclerosis. A giant cell tumor recurrent after curettage or infected from biopsy is a less satisfactory object for treatment than is the uncomplicated lesion. Furthermore, recurrences may be fully malignant. Some giant cell tumors appear unusually aggressive and locally malignant from the start. This feature cannot be regularly predicted from small biopsy specimens. If an attempt is made to treat these varieties with small doses calculated to control the usual giant cell tumor, they may become resistant to irradiation. These patients usually undergo amputation, occasionally too late to prevent metastases. Not all types of giant cell tumors do equally well under radiation. Large tumors of the upper end of the femur or tibia often do badly. It is my impression that giant cell tumors of the weight-bearing bones in older persons give poorer reactions to radiation than similar tumors in younger persons. Giant cell lesions of the jaw (I do not mean epulis) are satisfactory tumors for radiation. The multiple giant cell lesions occasionally seen involving the extremities of numerous long bones may be radiosensitive and regress with little treatment. The radiologist who treats these lesions must realize that as a rule he is not planning a course of therapy designed to cause regression of a malignant tumor of the bone. He is endeavoring to promote the sclerosis of a peculiar type of tumor, by no means always progressively destructive, often tending to considerable spontaneous fibrosis and repair.

The rare examples of cartilaginous variants of giant cell tumors at the upper end of the humerus have done well after irradiation. They tend to undergo sclerosis and to lay down calcium, much as do other giant cell tumors. These tumors have been confused with malignant chondrosarcomas, but deserve a separate grouping (Codman<sup>107</sup>). I believe that the telangiectatic varieties of benign giant cell tumors, the aneurysmal type, are less radiosensitive. Judging from structure and comparison, it is assumed that the xanthomatous variants are sensitive. When a giant cell tumor has broken through its capsule and is extending out into soft tissues, it is much less satisfactory to treat. It is much more difficult to produce the desired sclerosis. We have noted especially that when giant cell tumors of the acetabulum produce sufficient softening to permit driving the head of the femur up through the acetabulum, the results of irradiation are apt to be unsatisfactory. So many clinical features are involved in the question of irradiation regression of giant cell tumors that categorical statements are difficult.

Irradiation osteitis complicates the irradiation of many malignant tumors of the bone. After more severe irradiation, such as falls within the upper limits of therapeutic measures now commonly employed, there

107. Codman, E. A.: Surg., Gynec. & Obst. 52:543, 1931.

may be established a progressive productive osteitis which may cause marked thickening of the shafts at the expense of the marrow cavity, and in the case of cancellous bone may largely replace the fat and cellular marrow by poorly formed and brittle bone or calcified osteoid tissue. There are increased fragility of the lamellar bone and a marked tendency toward spontaneous fracture. The bone is almost devoid of circulation.

Complete devitalization may occur. The marked susceptibility of bone is probably due to the action of secondary rays on the delicate cell processes lying in the canaliculi, and secondarily to physical changes in the composition of the lamellae of the bone (Ewing<sup>108</sup>). Regaud<sup>109</sup> found that irradiation necrosis of bone is characterized by a long delay in sequestration. These features are probably due to sclerosis of the blood vessels of the haversian systems. Bone devitalized by radiation is extremely susceptible to infection with spreading suppurative periostitis.

Sclerosing osteogenic sarcomas are extremely radioresistant.<sup>110</sup> They are unsuitable for irradiation. Osteogenic chondrosarcomas may show temporary regression under massive doses. Relief from pain may be striking. Calcification may occur in projecting tumors of the soft parts and the radiologist may be deluded into believing that he is controlling the process. Then, almost uniformly, after a period of a few months, the pain recurs, growth is resumed, and the patient undergoes amputation, even though only palliative, for the relief of pain, which becomes intolerable. Periosteal osteogenic sarcomas, although less resistant than the sclerosing varieties, are nevertheless fully resistant. The cellular, telangiectatic small cell osteogenic sarcomas are apt to show pronounced regression with irradiation. In some instances this regression has been so marked that, on the basis of response to radiation, a clinical diagnosis of endothelial myeloma has been erroneously made. Such tumors show a cellular small spindle cell or polyhedral cell structure and may closely resemble endothelial myelomas. Large spindle and giant cell telangiectatic osteolytic tumors fail to show appreciable regression with irradiation. Destructive osteolytic sarcomas of the bone (fig. 31) regularly recur after primary regression. Despite the radioresistance of osteogenic sarcomas as a group, it is frequently possible, in the presence of metastases, to cause sufficient relief from pain by irradiation to enable the patient to avoid amputation. Mention must be made of occasional unusual successes in the control of osteogenic sar-

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108. Ewing, James: *Acta radiol.* 6:399, 1926.

109. Regaud, C.: *Compt. rend. Soc. de biol.* 87:427 and 629, 1922

110. Ewing, James: *Report of the International Conference on Cancer*, New York, William Wood & Company, 1928, p. 365.

coma. Such successes are rare. Several have occurred in the central spindle cell myxosarcomas of the calcaneus in young patients. In 1 instance both the primary lesion and a solitary pulmonary metastasis were sensitive, and there is reason to believe that life was appreciably prolonged. Despite rare successes, I have not been impressed with the results of irradiation of osteogenic tumors save as a palliative measure.

Most endothelial myelomas (fig. 32) are highly radiosensitive. Occasionally one sees a resistant endothelial myeloma. The reason for

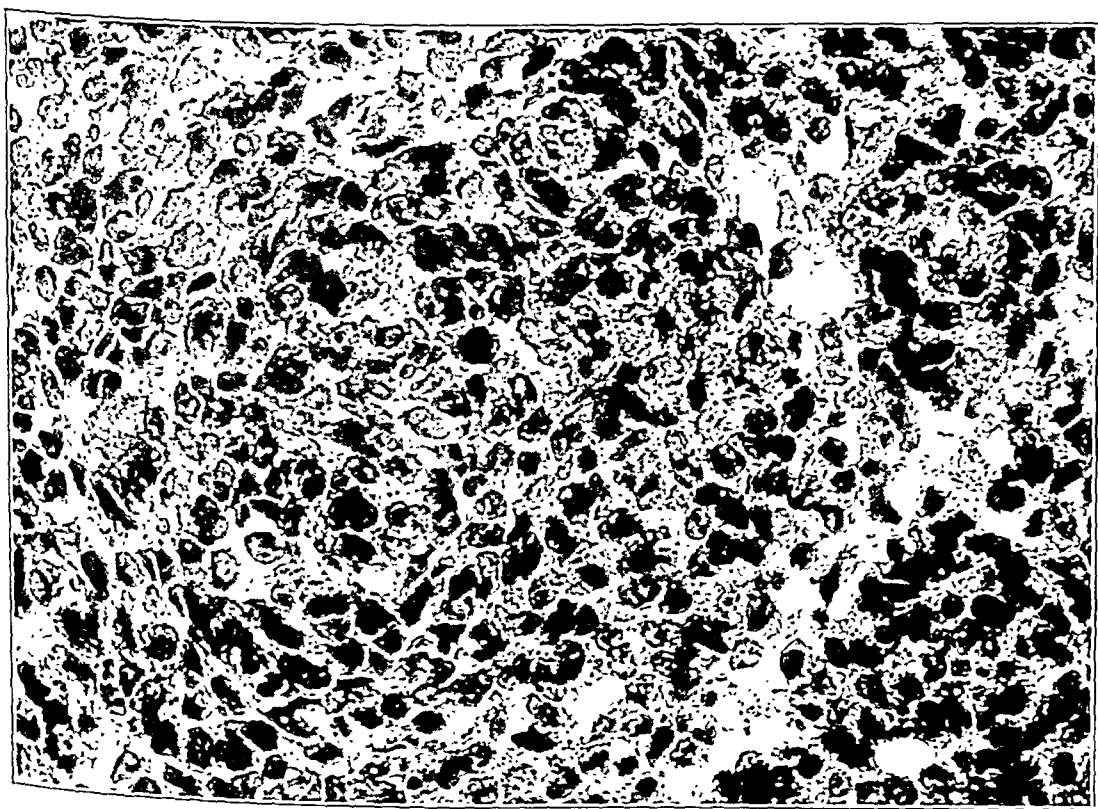


Fig. 31.—Bone; osteolytic osteogenic sarcoma; very cellular; cells rather small; delicate blood supply, yet radioresistant.

the resistance in certain cases is unknown. We have found an unusual circulation consisting of well defined, thick-walled vessels in resistant endothelial myelomas and believe that these circulatory conditions militate against sensitivity. The metastases are apt to be very sensitive. Most endothelial myelomas recur after irradiation. In many of the earlier patients treated at the Memorial Hospital the initial regressions were of such order that the clinician was lulled into false security. Under present methods of treatment recurrence is the rule. I believe that there should be a decided change in the method of irradiating these

tumors, and that massive doses should be replaced by divided irradiation as in the case of the sensitive intra-oral lesions. The best result I have personally observed was secured by that method. The various myelomas, plasmocytoma, myeloblastic myeloma and lymphoid myeloma, are exceedingly radiosensitive. I observed marked sensitivity in 2 probable reticulum cell lymphosarcomas of the bone (fig. 33). In neither of these cases was I certain of the diagnosis, yet from the histology it seemed most probable. It is possible that 1 of the tumors was of extra-

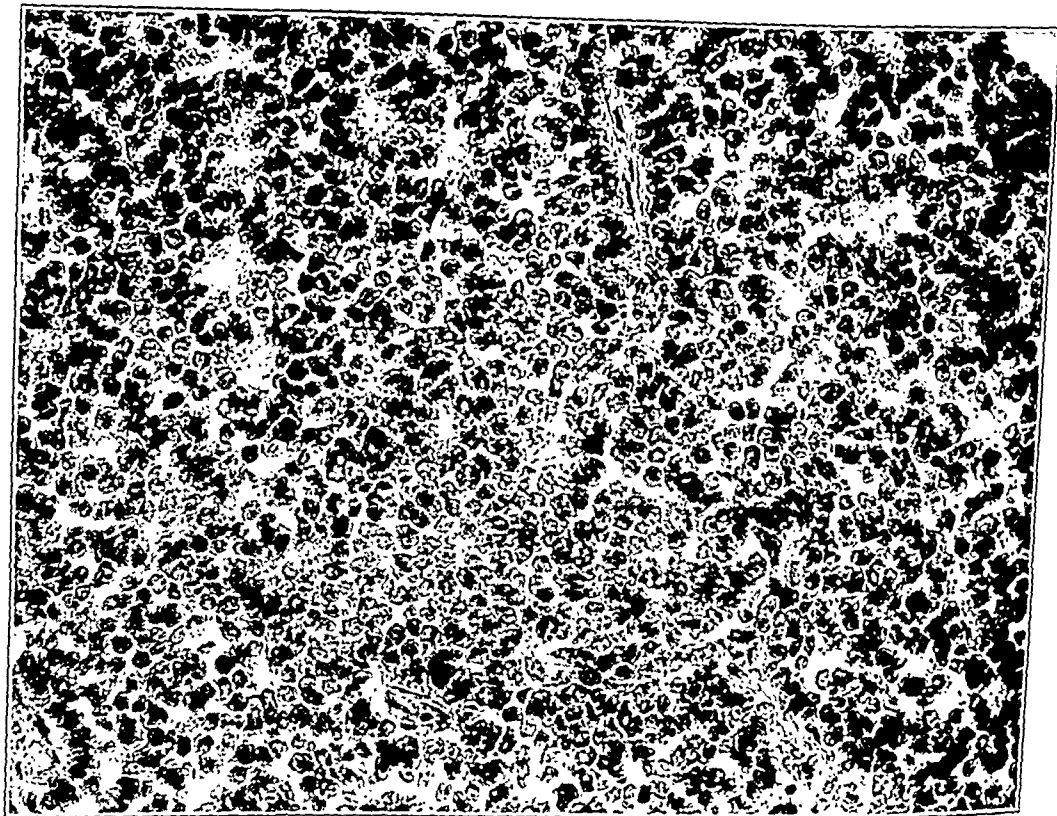


Fig. 32.—Bone; very radiosensitive endothelial myeloma (Ewing tumor).

osseous origin, probably lymphosarcoma of the abdominal lymphoid structures, since signs of abdominal tumor developed about one year after treatment, and the patient died. No autopsy was obtained.

The known metastatic lesions of lymphosarcoma, when they occur in bone, are radiosensitive. Hodgkin's disease in bone is common. It is apt to be radiosensitive. Frequently, however, the process is sclerotic. The lesions of the bone may occur early in the course of the disease or may be late manifestations. When extensive, anemia is usually marked, and the patients are unsatisfactory subjects for treatment. Hence, the sensitivity is but rarely of more than academic interest.

Liposarcomas of the bone are rare. I<sup>111</sup> described 3 cases. Since that time several have appeared in the Bone Sarcoma Registry of the American College of Surgeons. The cases from the Memorial Hospital were from moderately to markedly radiosensitive. One was so sensitive that the tumors were reduced to nothing but masses of blood clot.

The xanthomatous "tumors" of Christian's syndrome (diabetes insipidus, exophthalmos and multiple xanthomatous tumors of mem-

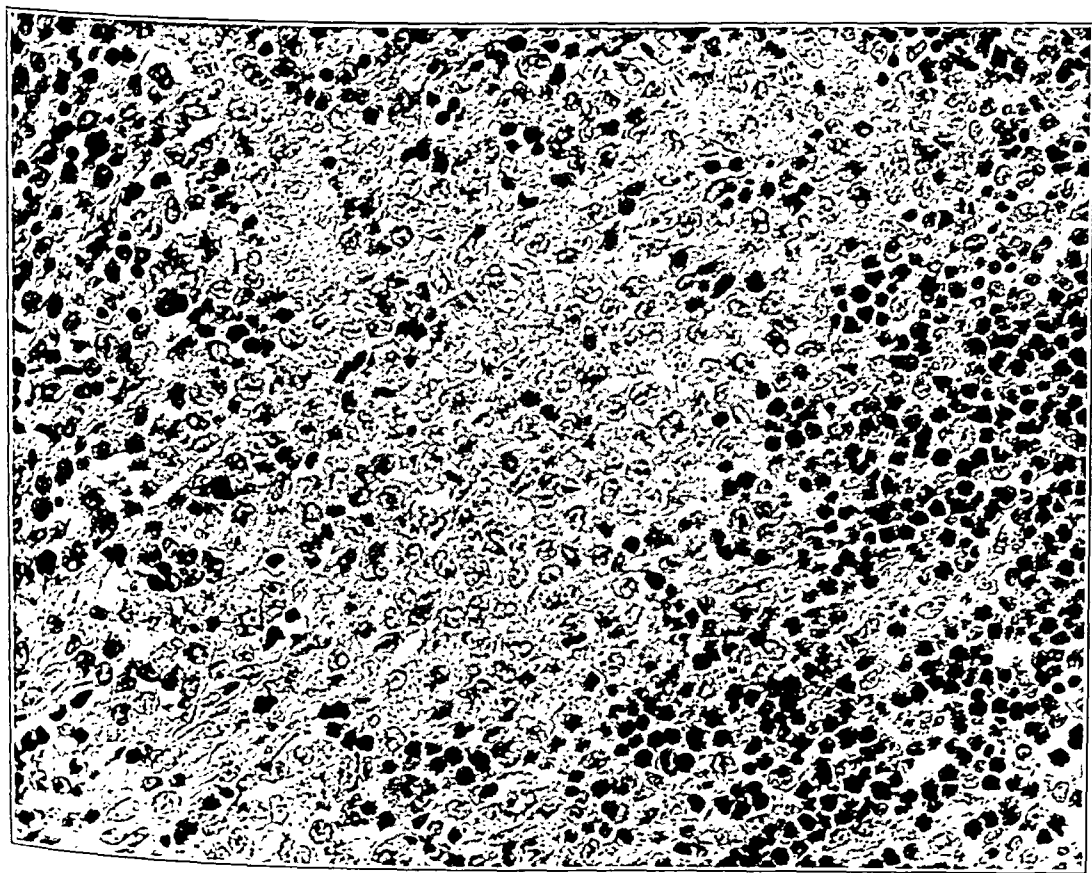


Fig. 33.—Bone; very radiosensitive primary reticulum cell sarcoma.

brane bones) are favorably influenced by radiation; the bone defects tend to heal. They regress under small doses (Rovida<sup>112</sup>).

#### NEUROGENIC SARCOMA

Tumors variously designated as neurogenic sarcomas, neurinomas, schwannomas, peripheral gliomas and perineural fibroblastomas are radioresistant (Stewart and Copeland<sup>113</sup>). Certain rapidly growing

111. Stewart, F. W.: *Am. J. Path.* 7:87, 1931.

112. Rovida, Francesco: *Radiol. med.* 19:667, 1932.

113. Stewart, F. W., and Copeland, M. M.: *Am. J. Cancer* 15:1235, 1931.



tumors clinically diagnosed at the Memorial Hospital as neurogenic sarcomas have shown marked sensitivity. No sections were made, and when these results are compared with results in patients for whom histologic diagnoses were available, they are far from striking proof of the sensitivity of this disease. Even very cellular, small cell, neurogenic tumors (fig. 34) have grown under radiation. Any favorable response usually requires large doses. Interstitial radium has cured a

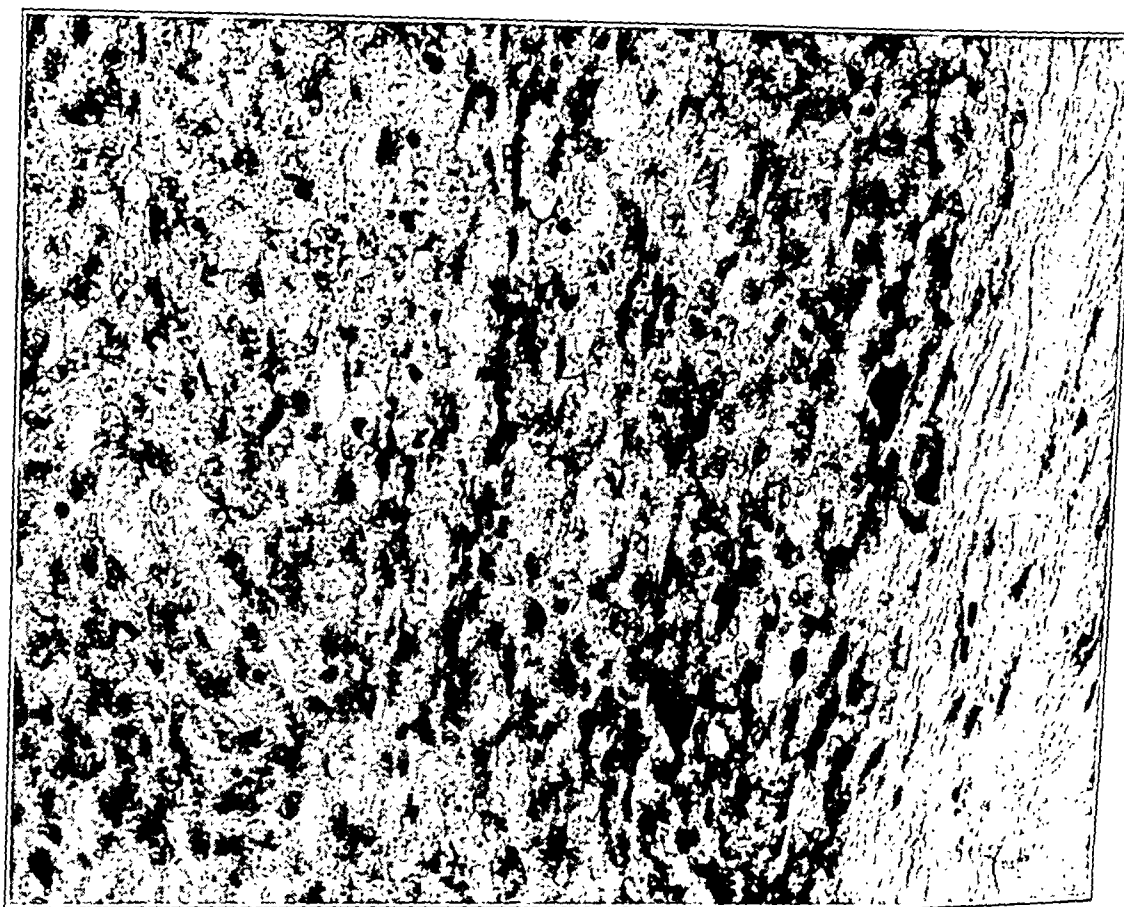


Fig. 34.—Neurosarcoma of median nerve. Very cellular; cells seem to possess certain embryonal qualities, yet are highly radioresistant.

few patients. The difficulty with its use is usually that the tumors, when first seen by the radiologist are too large to permit efficient distribution of adequate quantities of radium. Furthermore, such treatment results in cure by irradiation and is not in itself indicative of any particular degree of radiosensitivity. External irradiation has caused disappearance of an occasional tumor to the accompaniment of prolonged slough of normal tissues. The successful irradiation of neurogenic sarcoma converts the mass into indolent scar tissue, extremely dense and hyaline. This mass undergoes progressive atrophy. A few low

grade neurogenic sarcomas, differing little in histologic structure from neurofibromas, will show slow progressive regression and eventual disappearance after doses of external irradiation well tolerated by the normal structures. Yet these cases seem to be few.

The natural history of a neurogenic sarcoma is such that it is virtually impossible to say whether a new mass in the irradiated field is a

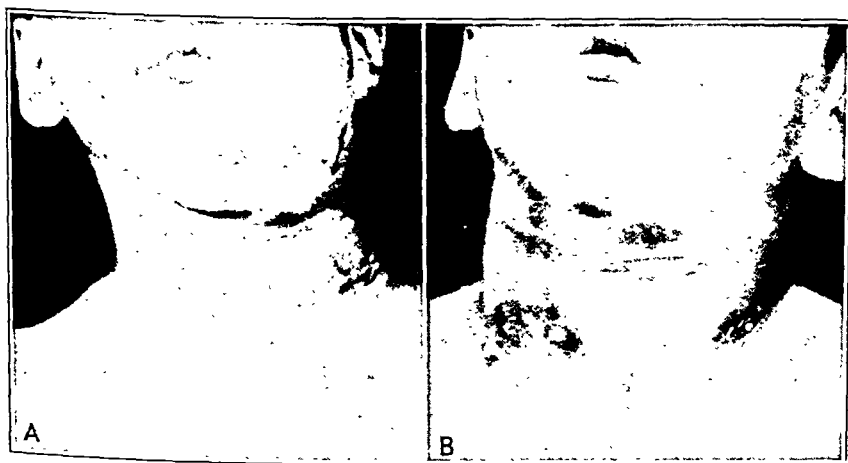


Fig. 35.—Ganglionic neuroblastoma, probably arising in cervical sympathetic: *A*, before irradiation; *B*, after irradiation.



Fig. 36.—Ganglionic neuroblastoma metastatic to lungs: *A*, before irradiation; *B*, after irradiation. The tumor recurred and caused death.

new tumor or a recurrence in the usual sense. The tumors are frequently of multicentric origin, arising from numerous nerves in a locus. If one examines an excised neurogenic tumor, it may be possible to find the initial changes leading to new tumors in the surrounding nerves excised with the primary mass. This might lead one to suppose that external irradiation might be used after operation to restrain the growth

of tumor masses originating from surrounding nerves in the scar or in the adjacent territory, yet Stewart and Copeland, in a large series of cases, could not find evidence that such irradiation was efficacious. The irradiation of neurogenic sarcomas is a highly unsatisfactory field. Surgical intervention is equally so. Perhaps in no other field of neoplastic diseases is a comparatively innocent looking tumor from the histologic standpoint so fraught with ultimate danger to the patient.

The reason for the radioresistance of neurosarcomas is not clear on a histologic basis alone. Many of the tumors show all the features which might lead one to believe they were sensitive. Their resistance is probably to be interpreted in the light of their neural origin and in the light of the well known great radioresistance of nerve tissue. The neuroblastomas, tumors made up of small neuroblastic rosettes or containing large numbers of poorly developed ganglionic elements, do not share the usual resistance of neurogenic tumors. The retroperitoneal and suprarenal groups are highly sensitive. I have observed recently a ganglionic neuroblastoma probably arising in the cervical sympathetic ganglions in a young boy. Under irradiation, the tumor proved as sensitive as a lymphosarcoma. Large pulmonary metastases filling much of the chest regressed dramatically, recurred and regressed again until the patient could tolerate no further treatment (figs. 35 and 36).

#### "FASCIAL" SARCOMA

Fascial sarcomas constitute a complex group of variable histology and probably different histogenesis. They are spoken of as fascial sarcomas largely because their exact histologic origin is not readily determined. Some exhibit a structure resembling periosteal, nonossifying sarcoma. Others probably originate in fat tissue. Some are neurosarcomas. There is reason to believe (Stewart and Copeland) that many of the extraperiosteal fibrosarcomas are of neurogenic origin, since the patients may have either stigmas of von Recklinghausen's disease or other sarcomas clearly of neural origin. There is a group of myxosarcomatous tumors made up largely of almost acellular mucin, their cellular elements consisting mainly of capillaries and sprouting endothelial buds. They may have a telangiectatic circulation. Necrosis and cystic degeneration are common. Some appear grossly to consist in structureless jelly masses. They may occur anywhere. The sole seems to be a favorite location. Since the active elements consist almost wholly of vascular sprouts, the lesions may show a decided restraint of growth under irradiation. Actual total regressions are rare. The extraperiosteal tumors of neural origin show the resistance of neurogenic sarcomas. In general, the irradiation treatment of the tumors is unsatisfactory.

## RHABDOMYOSARCOMA

Rhabdomyosarcoma is a rare tumor. In the few patients with this disease who have been treated at the Memorial Hospital, the tumors have been radioresistant.

## LIPOSARCOMA

Malignant tumors of fat tissue afford the radiologist a happy relief. Contrary to the behavior of the majority of the sarcomas of the soft parts, these tumors usually show from moderate to marked radiosensitivity. There is no good explanation for such sensitivity. The tumors may consist of rather well developed, adult-looking fat cells. There is nothing inherent in fat tissue which would make one suppose that tumors of the fat tissue would be radiosensitive. The cells consist of narrow rings of cytoplasm filled with fat, which compress the nucleus toward the periphery of the cell. The metabolism of fat tissue is not considered active. Under interstitial irradiation, fat tissue breaks down, forming oil cysts and producing an indolent inflammatory tissue with giant cells of the foreign body type. Fibrosing, sclerosing reactions are poorly developed, rendering fat tissue a poor medium for restraint of growth. Nevertheless, even when these liposarcomas are made up of adult-looking fat cells, they are relatively radiosensitive (fig. 38).

Certain liposarcomas have a cellular structure made up of from small to medium-sized hyperchromatic polyhedral cells (fig. 37). They show other areas of nearly purely xanthomatous or xanthosarcomatous structure. Such tumors are highly sensitive, and yet are apt quickly to yield diffuse metastases. Other tumors reveal bizarre pseudo-alveolar formations, with large fat-filled or xanthomatous giant cells. More adult-looking liposarcomas often show myxomatous degeneration. They may occur anywhere in the soft tissues, subcutaneous, fascial or muscular—where it may be difficult to distinguish them from angiomas of the muscle, since they are extremely vascular—in the orbit, especially about the knee joint and in the retroperitoneal region of the perirenal fat tissue. Fairly adult-looking tumors may yield distant subcutaneous metastases. The small round to polyhedral cell lipogenic tumors may yield to doses little more than sufficient to cause regression of the more resistant lymphosarcomas. They have been cured by radiation even when bulky postoperative recurrences were present.

## SYNOVIAL TUMORS

Tumors of the synovial membrane are complex and imperfectly analyzed. They may exhibit a mixed structure, suggesting in part an origin from synovial mesothelium, and in other portions an endothelial or perithelial origin. Some suggest a relation to the giant cell tumors of tendon sheath origin. Others have a xanthosarcomatous or liposarcomatous element. Some are so cellular and composed of indifferent

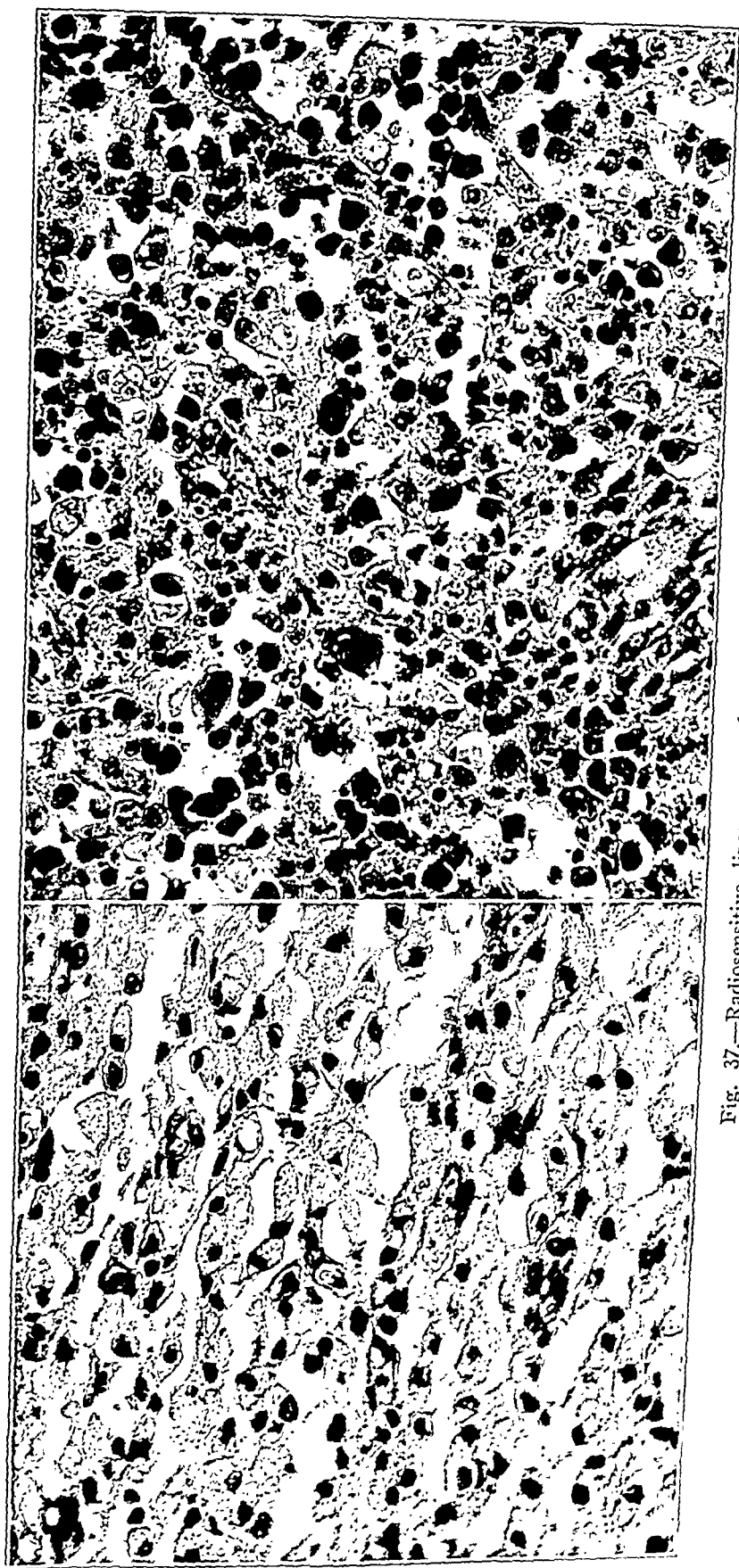


Fig. 37.—Radiosensitive liposarcoma of subcutaneous tissues.

round cells that only radiographic evidence permits their distinction from endothelial myelomas. The more malignant varieties recur in amputation stumps, and rapidly yield pulmonary metastases. They may, in contradistinction to most sarcomas of the soft parts, metastasize to nodes. Many of these tumors appear radiosensitive, and yet with the doses so far utilized in their treatment at the Memorial Hospital they have not yielded satisfactory results. No definite opinion can be expressed as to their radiosensitivity until they have been handled more aggressively than has hitherto been the case. It seems safe to

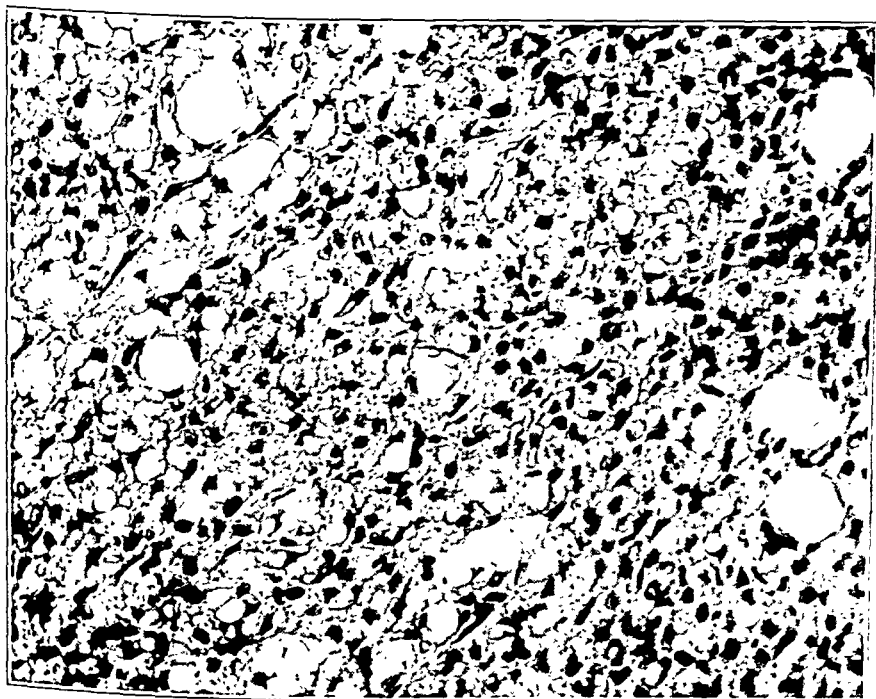


Fig. 38.—Radiosensitive liposarcoma; rather adult fat cells. Primary tumor and metastases radiosensitive.

admit, however, that their response to radiation will not be of the nature of a dramatic disappearance of growth.

#### MELANOMA

The records of the Memorial Hospital contain about 250 cases of melanoma. These tumors are almost uniformly highly radioresistant. About 2 per cent have some degree of sensitivity. There is nothing in their structure which permits a diagnosis of radiosensitivity. They are apt to be as resistant or even more resistant than the surrounding normal tissues and may sprout up under sufficient interstitial irradiation to destroy the tumor bed. Fulminating, widespread, hematogenous metastases to the skin and subcutaneous tissues may be sensitive. In fact, their occasional instability is revealed in the rare spontaneous dis-

appearance of nodules here and there. Such sensitivity is of no therapeutic interest. After prolonged attempts at the irradiation treatment of melanoma, I believe that once the course of the disease is established in the direction of the lymphatic rather than the hematogenous mode of dissemination, aggressive surgical intervention is far better than irradiation. The most satisfactory regressions with irradiation in my personal experience have been in the conjunctival group. Whether or not there is a regional peculiarity in the behavior of the disease in this location must be determined from further experience. The probability is that the results were merely due to beta irradiation of superficial lesions and not to any unusual radiosensitivity.

#### ANGIOMA

Angioma occurs in a variety of types. Naturally, these various lesions differ in their response to radiation. There are the simple spider angiectases which yield to small amounts of beta radiation. There are the simple port wine nevi which blanch with radiation, especially in young subjects, but which tend to become more resistant with increasing age. Another variety constitutes the hemangioma hypertrophicum cutis. These lesions are often bulky and exuberant-looking in sections, and may suggest angiosarcomas. They are only moderately radiosensitive. The bulky, deeper angiomas, especially when aneurysmal features are present, are relatively resistant tumors. They do not do well with radiation, save when it is administered by interstitial means. Then they may yield by thrombosis and local sclerosis, a gradual cutting down of the circulation and not true radiosensitivity. The angiomas of the Osler-Rendu-Weber type present a variety of structures. Different anatomic forms must act differently under radiation. Little is known concerning the behavior of true angio-endotheliomas. In the literature this is a common diagnosis. In our own laboratory we rarely see such cases. The angio-endothelioma of Kaposi (multiple hemorrhagic sarcoma) shows considerable variation in its response to radiation. Most cases of this disease are radioresistant. In one patient regression of the tumors required doses sufficient to sterilize squamous cancer. Furthermore, there was no assurance that the disease would not recur at the immediate periphery of the treated area. Whether this was recurrence in the true sense or merely the result of the continued presence of some causative agent cannot be determined. This case, like several other Kaposi types we have studied, behaved like a true infectious disease with, however, a distinctly neoplastic histology. In other patients the presence of marked infection has obscured the response to irradiation. Some cases of Kaposi's disease have yielded to the x-rays (Collins<sup>114</sup>). For that matter, some lesions appear to

114. Collins, J. N.: *Am. J. Roentgenol.* 26:269, 1931.

regress with no treatment. Tumors of the glomus type (Masson's angiome neuromyoartériel) have so far appeared relatively radio-resistant.

Lymphangioma is quite a different problem. The lymphangiomas are highly radioresistant. Their resistance is probably an expression of the well known resistance of lymphatics to radiation (Wood<sup>14</sup>).

#### SQUAMOUS AND BASAL CELL CARCINOMAS OF THE SKIN

The squamous carcinomas of the skin do not appreciably differ in their behavior to radiation from those of the lips, oral mucous membranes and cervix. Hence they are omitted from further discussion. Basal cell epitheliomas (tricho-epitheliomas of Regaud and others) are relatively radiosensitive lesions. When adenoid features develop the tumors become more resistant, and, in the vast majority of cases, when the structure of adenoid cystic epithelioma is approached, they are very resistant. The behavior of the usual basal cell epithelioma is greatly dependent on the tumor bed. Nothing is more resistant than the basal epithelioma invading bone or cartilage; hence their evil prognosis when they have attained any decided degree of infiltration about their common site, the face. Long experience with basal cell epitheliomas (there were 1,374 patients with this disease treated in Memorial Hospital in the twelve year period of 1917 to 1929) has taught us that previous insufficient irradiation of a basal cell lesion increases the resistance of the carcinoma and diminishes that of the tumor bed, thus eventually leading to an undesirable set of circumstances. It is believed highly desirable to destroy the lesion at a single exposure.

#### LYMPHOMA, LYMPHOSARCOMA, LYMPHOGRANULOMA, LEUKEMIA

The radiosensitivity of lesions of the lymphoma group is so well known in every institution where radiation is administered that it seems scarcely worth while to reemphasize it in the present paper. The malignant lymphocytomas and reticulum cell lymphosarcomas are highly radiosensitive. Rarely one encounters a relatively radioresistant lymphosarcoma, and the disease progresses with great rapidity. Under such circumstances the structure is often that of giant reticulum cell sarcoma. It is difficult to explain the occasional resistance of the lymphosarcoma. In many respects the disease is peculiar. It involves, usually at the onset, a small group of nodes. The surrounding nodes may exhibit varying degrees of giant follicular hyperplasia. It is well understood that the normal lymph node is a relatively resistant structure. It is possible that in treating lymphosarcoma one causes regression of the diseased nodes, but that in response to the continued



exciting stimulus new closely adjacent nodes are brought into neoplastic activity thereby simulating a recurrence? The actual cure of lymphosarcoma is an extreme rarity unless one accepts the statistics of Berven on tonsillar lymphosarcoma. Berven<sup>35</sup> reported many apparent cures of tonsillar lymphosarcoma, so many in fact that one wonders whether some were not cellular lympho-epitheliomas of the Schmincke type. Berven stated that in many of his patients the tonsil was large and ulcerated. At the Memorial Hospital we find actual ulceration rare in cases of tonsillar lymphosarcoma but common in those of lympho-epithelioma. Incidentally, many tonsillar tumors which five years ago we should have called lymphosarcomas we now recognize as lympho-epitheliomas.

The lymphadenomas of the Brill-Symmers type are very radio-sensitive. The lesions of the lymph nodes in lymphatic leukemia are also sensitive, especially when they approach the structure of lymphocytoma. When merely of the hyperplastic type, as in pseudoleukemia, they are somewhat more resistant. Mikulicz' syndrome on a leukemic basis is very radiosensitive. The simple lymphomas vary extraordinarily in their responses to radiation. This variation cannot be accurately predicted from their microscopic appearance.

The lesions of the lymph nodes in Hodgkin's disease are often highly radiosensitive, although somewhat less so than lymphosarcomas. In the sclerosing, fibrotic lesions radioresistance is the rule. Some authors report the cure of Hodgkin's disease by radiation. At the Memorial Hospital we have had no cures in cases in which the diagnosis was confirmed in our own laboratory and in which the lesion was typical. In passing it may be well to note that "prophylactic" irradiation of uninvolved areas does not prevent later involvement.

The sensitivity of the various lesions of myelogenous leukemia is well known. This sensitivity is so marked that it may occasionally lead to disaster. We have seen radiation convert a leukemic spleen into a massive thrombosed hematoma, followed by death from embolism. The bulky deposits in the nodes, which may occur late in leukemia as a result of embolic myeloidization of the nodes, are radiosensitive. This lesion is supposedly rare, yet I found it to a marked extent in 4 successive leukemic autopsies during the current year. The sensitivity of such deposits in the lymph nodes is not of therapeutic interest, since it marks a terminal phase of the disease.

That there are differences in the radiosensitivity of the various cell types in the blood-forming organs was early shown by the studies of Heineke.<sup>115</sup> He found that after irradiation the various white cells disappeared from the marrow in the following order: (1) lympho-

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115. Heineke, H.: *Deutsche Ztschr. f. Chir.* 78:196, 1905.

cytes, (2) nongranular mononuclear cells, (3) eosinophils, mast cells and giant cells, (4) myelocytes and polymorphonuclears. The erythrocytes were "nur wenig geschädigt" (only slightly injured). Casati<sup>116</sup> irradiated the bone marrow of rabbits, giving doses of 400 roentgens once repeated. He found no clear changes prior to two weeks after irradiation. He stated that the myelocytes differentiate to polymorphonuclear cells and that the myeloblasts change to fibroblasts. In case there is no regeneration of myeloblasts, the marrow becomes fibrotic. More recently Sabin, Doan and Forkner<sup>117</sup> found, after intravenous injection of radioactive materials (radium chloride and mesothorium), that the bone marrow as a hematopoietic organ is less sensitive than the lymph nodes. They expressed the belief that with certain doses of radio-active material, the fundamental damage in the lymphoid tissue is to the stem cell and especially to the nuclear chromatin of these cells. They described a period of stimulation of the stem cells; second, a shift to the immature stage known as the lymphoblast; third, a depletion of the nodes due to such damage to the stem cells that the losses in lymphocytes could no longer be made up. The studies of Sabin, Doan and Forkner indicate that the thymic cells are affected in the same manner as the primitive stem cells of the lymph nodes, and that they are less resistant to radiation than the mature lymphocytes. The concept of particular effects on the special formative cells of the lymph nodes is of considerable interest to the radiologist and fits well with the concept of the particular effect on the "cellules souches" in many tumors.

#### THYMOMA

Thymoma is frequently diagnosed radiographically. Our observations coincide with those of Haagensen, that it is not so simple to verify a diagnosis of primary thymoma at autopsy. Many tumors which throw shadows suggestive of thymoma and which regress promptly under irradiation only to return at a later period fail to show a gross anatomy definitely indicative of thymic origin, although bulky masses occupying a position in the anterior mediastinum over the great vessels at the base of the heart are certainly suggestive of thymic origin. At times the bronchial and hilar nodes may be involved in contiguity with the pericardial mass, and it becomes impossible to verify the thymic origin.

It seems assured that thymic tumors may have a multiplicity of structure, such as lymphocytomas, reticulum cell sarcomas (fig. 39), large atypical lymphosarcomas, Hodgkin's sarcomas and granulomas.

116. Casati, Annibale: *Strahlentherapie* 32:721, 1929.

117. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: *J. Exper. Med.* 56:267, 1932.

true carcinomas (figs. 40 and 41) of varying type, either anaplastic large polyhedral cell tumors or carcinomas with many Hassall's corpuscles. It is probable that lymphosarcomas of the thymus behave much as lymphosarcomas elsewhere. They usually recur. At the Memorial Hospital there is a record of but a single prolonged cure, now nearly eleven years, of a patient with a bulky tumor, probably of thymic origin,

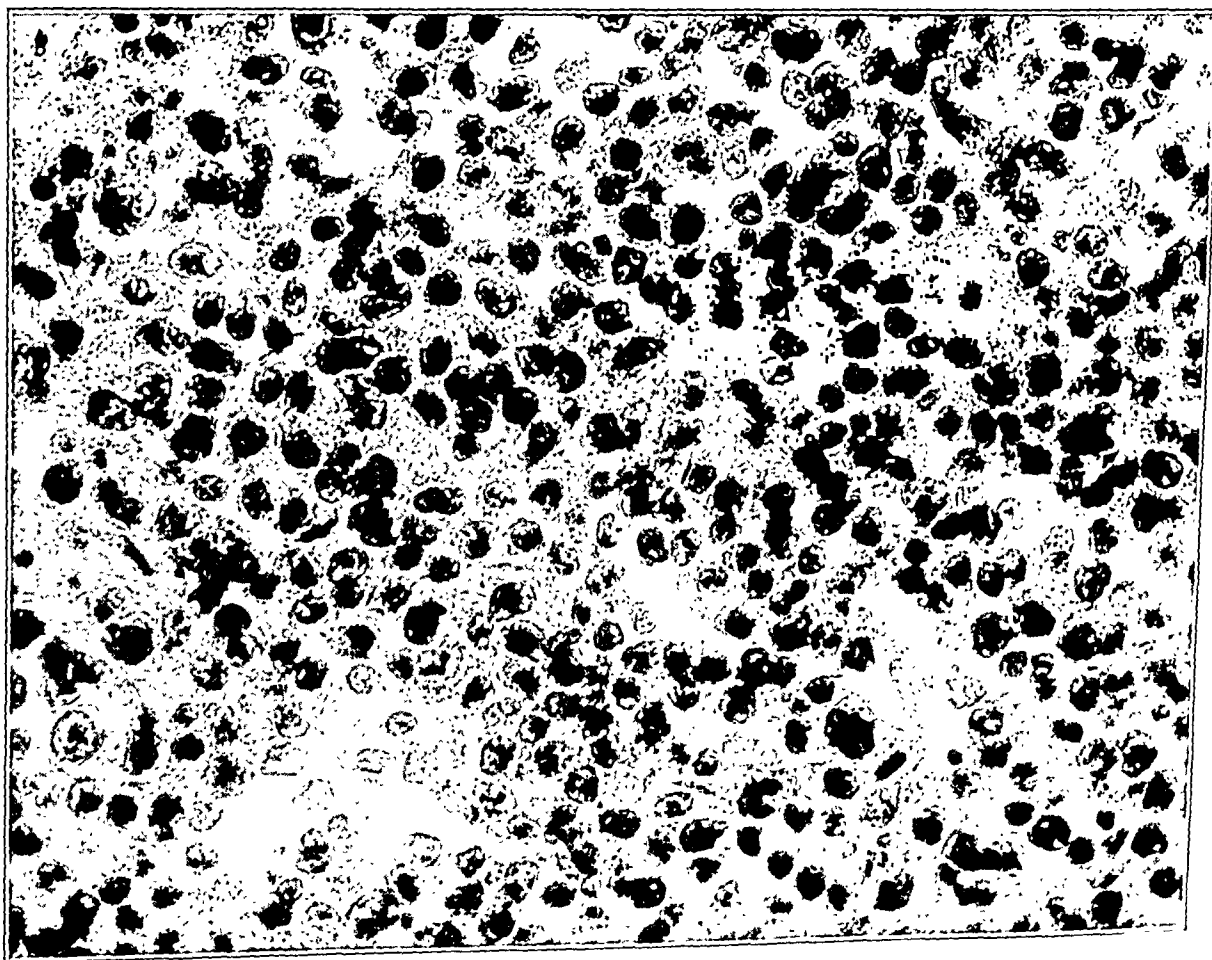


Fig. 39.—Radiosensitive mediastinal tumor; lymphosarcoma, possibly thymic.

which filled nearly the entire chest. This tumor vanished after a small amount of low voltage irradiation. The patient is well, and the result has never been duplicated. Haagensen<sup>118</sup> found that the small cell anaplastic carcinomas of the thymus show little benefit from radiation. One patient with thymic carcinoma containing many large Hassall's bodies showed some regression about on the order of that to be expected with a moderately sensitive epidermoid carcinoma, but nothing of striking character.

118. Haagensen, C. D.: *Am. J. Cancer* 16:723, 1932.

Some authors are so certain about the irradiation behavior of these mediastinal tumors that they offer differential diagnoses according to their responses to radiation. I feel considerable less certainty in the matter. Evans and Leucutia<sup>119</sup> expressed the belief that "tumors originating from proliferation of the lymphatic cell element—including lymphosarcoma, thymoma, lymphatic leukemia, pseudoleukemia and simple lymphoma—" entirely disappear within from four to ten days

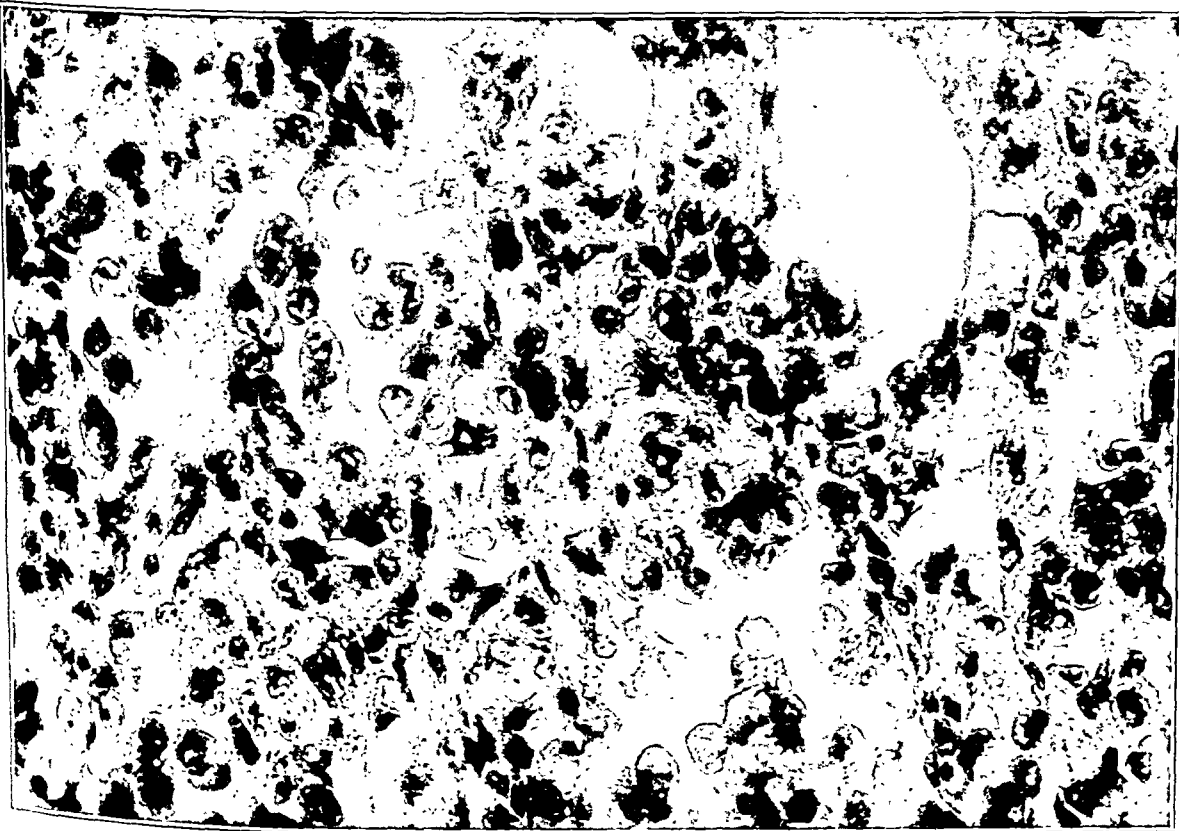


Fig. 40.—Radioresistant thymic carcinoma.

following one skin erythema dose of high voltage roentgen therapy. Tumors originating from proliferation of the reticulo-endothelial element of the mediastinal nodes or thymus, including Hodgkin's disease, Sternberg's type of hyperplastic tuberculosis and endothelioma, are reduced to half size in ten days and entirely disappear within five or six weeks. Primary carcinoma and sarcoma show more or less reduction in size, but rarely disappear within six weeks following irradiation

<sup>119</sup> Evans, W. A., and Leucutia, T.: Deep Roentgen-Ray Exposure, *J. A. M. A.* 85:1215 (Oct. 17) 1925.

with a similar dose. I regret to state that our observations fail to support the contentions of Evans and Leucutia as regards standardized type responses. Doub<sup>120</sup> reported thymomas sensitive to radiation. Lenk<sup>121</sup> found thymic cancer thoroughly resistant.

#### TUMORS OF THE BRAIN

Published reports indicate that on the whole tumors of the brain show little radiosensitivity. Thus, Bailey, Sosman and Van Dessel<sup>122</sup>

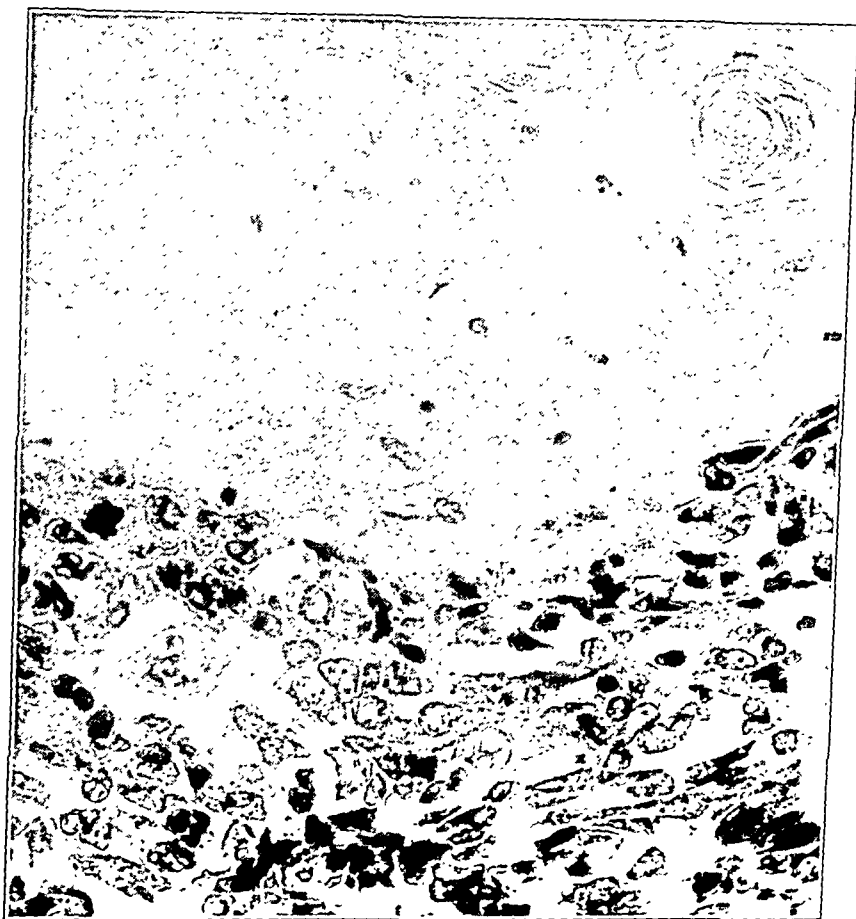


Fig. 41.—Thymoma with large hyaline Hassall's bodies. It is radioresistant, yet its lymphatic metastases tended to regress about to the same degree one would expect in the case of oral carcinomas of medium sensitivity.

stated that roentgen therapy will not cure any glioma. They recognized some favorable effect in medulloblastomas, a slight favorable

120. Doub, H. P.: *Radiology* **14**:267, 1930.

121. Lenk, Robert: *Die Röntgendiagnostik der intrathorakalen Tumoren und ihre differential Diagnose*, Berlin, Julius Springer, 1929.

122. Bailey, Percival; Sosman, M. C., and Van Dessel, Arthur: *Am. J. Roentgenol.* **19**:203, 1928.

effect, but less so, in spongioblastoma multiforme, a possible influence in astroblastomas and a slight effect in astrocytoma protoplasmaticum. Sargent and Cade<sup>123</sup> were somewhat more optimistic. They found the best irradiation results in astrocytomas and medulloblastomas. They found it difficult properly to assess the results in oligodendrogliomas. The response in spongioblastoma multiforme is variable. A few patients have secured complete regression of symptoms. I have had no personal experience whatever in the field of tumors of the brain and therefore cannot express an opinion.

In the case of pituitary adenomas with or without the acromegalic and Fröhlich syndromes, encouraging results have followed irradiation. Bécélère<sup>124</sup> stated that irradiation is the method of choice in pituitary tumors. He gave a wide review of the literature on this subject. Nemenow and Jugenburg<sup>125</sup> expressed the belief that (1) good results may be expected in adenomas of the anterior lobe; (2) good results may be expected when the Fröhlich syndrome is due to pressure on the intermediate and posterior lobe; (3) no results follow when tumors of the third ventricle and of the midbrain are present; (4) no result follows irradiation of suprasellar cysts. The authors stated that in some cases of radiosensitive pituitary tumors radiation will restore health and bring back vision when the subjects are almost blind.

#### ORBITAL AND BULBAR TUMORS

Very little systematic information is available on the behavior of various types of orbital and bulbar tumors following irradiation. The lymphomas may be radiosensitive; some are certainly resistant. Neurosarcomas of the orbit have been very resistant. Retro-ocular liposarcomas have given moderate regression followed by recurrence. The ocular melanomas are extremely radioresistant. In cases of neuroepithelioma of the retina and of retinoblastoma considerable regressions have followed irradiation. Recurrence is the rule. Some patients with retinal gliomas have been cured by external irradiation. The tumors were small. Irradiation seems most successful when after one of these usually bilateral gliomas has attained such a size that it becomes clinically discoverable attention is directed to the opposite eye, in which a small tumor is detected. Irradiation of these smaller tumors may result in cure with conservation of vision. Successes have been reported by Axenfeld,<sup>126</sup> di Marzio and Salvatori,<sup>127</sup> Moore<sup>128</sup> and Knapp and

123. Sargent, P., and Cade, S.: *Brit. J. Surg.* **18**:501, 1931.

124. Bécélère, Antoine: *Strahlentherapie* **31**:42, 1929.

125. Nemenow, M., and Jugenburg, Anna: *Strahlentherapie* **30**:239, 1928.

126. Axenfeld, in discussion on Hartung: *Klin. Wchnschr.* **9**:811, 1930.

127. di Marzio, Q., and Salvatori, G. B.: *Strahlentherapie* **43**:68, 1932.

128. Moore, R. F.: *Brit. J. Ophth.* **14**:145, 1930.

Lüdin.<sup>129</sup> Benedict<sup>130</sup> reported regression of retinoblastomas. Very large doses were required. A posterior cortical cataract occurred as a later complication.

#### CONCLUSIONS

My purpose has been to emphasize the complexity of the problem of radiosensitivity. I have called attention to the difficulties of establishing hard and fast rules. I have encouraged the notion that ideas of tumor sensitivity may change with changes in radiologic technic. I have called attention to the need of expressing response to radiation in terms of dosage. Peculiarities in the behavior of certain tumor types have been noted, and differences in the responses of apparently similar tumors in different regions have been discussed. Much of the paper has unfortunately been devoted to the statement of observed facts, which are often wholly unexplained. It is difficult to summarize in a few sentences material which many pages have but incompletely described, yet since some crystallization is necessary, the following brief paragraphs may serve.

1. Radiology is an active science. Ideas and methods are constantly changing. As methods change, notions of what may be expected from irradiation of tumors will also change. For example, if current ideas of radiosensitivity were derived wholly from observations made in the days when the low voltage x-rays represented the entire therapeutic armamentarium, then sensitive tumors would be rare and the field of radiology limited. Improved methods, while they alter no fundamental principles, constantly widen their applicability to the advantage of the patient with cancer.

2. Radiosensitivity may mean rapid tumor regression, slower progressive regressions over a period of from days to weeks or slow chronic atrophy requiring months or perhaps a year for completion. Of course, the same mechanisms are not responsible for these various responses, nor do they occur in the same types of tumors. Radio-sensitivity does not mean the certainty of cure by irradiation, nor does radioresistance imply that a given tumor is not curable by irradiation.

3. Certain tumors seem to possess inherent properties of radioresistance, as witnessed, for example, in the melanomas and neurogenic tumors.

4. Radiosensitivity increases with increasing embryonal quality of the tumor cells. By embryonal quality I do not imply that all tumors of embryonal origin are equally radiosensitive, since embryonal qual-

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129. Knapp, Paul, and Lüdin, Max: *Klin. Monatsbl. f. Augenh.* **83**:279, 1929.

130. Benedict, W. L.: *Retinoblastoma in Homologous Eyes of Identical Twins*, *Arch. Ophth.* **2**:545 (Nov.) 1929.

ity is a relative attribute and many embryonal tumors rapidly acquire adult characteristics, for example, the complex teratomas.

5. Radiosensitivity increases with the increasing degree of anaplasia. This rule is subject to interpretation, for not all anaplastic tumors are radiosensitive. Some are highly resistant, and unless the exact type of anaplastic tumor is specified, anaplasia may be of little significance.

6. Radiosensitivity is always a relative property. When one states that a carcinoma of the breast, for example, is radiosensitive, one should imply that it is sensitive according to the accustomed scale of behavior of tumors of the breast and not according to the same scale of sensitivity one applies to lymphosarcoma.

7. Tumors are apt to be more sensitive in young subjects. An anemic or cachectic person is a poor subject for radiation.

8. Infection interferes with a normal response to radiation.

9. Desmoplastic tumors are apt to be radioresistant.

10. The tumor bed is of great importance. A normal tumor bed is generally favorable. Bone, cartilage and fat make unfavorable mediums for reactive processes and hence for regression of the tumor. An avascular bed is unfavorable for response to radiation.

11. Tumors, when metastatic to lymph nodes, may be more or less sensitive than the primary tumors. This phenomenon is not fully explained. Metastases to the lymph nodes, long established, tend to be less sensitive than recent emboli. The old metastasis has had time to acquire its definitive blood supply and to adapt itself to its new surroundings, while the recent embolus is still foreign to its new soil. A recent, rapidly growing metastasis is more apt to be unstable than a smaller metastasis of longer duration. Cystic nodes are apt to be resistant.

12. Bulky tumors may become resistant after infarction and liquefaction, even though they belong to usually sensitive types. This may be due to the fact that fibrosis proceeds slowly and inefficiently under such conditions. The cells in the liquefied areas are removed from restraining fibrosis. The same explanation may be applied to the resistance of tumor cells lying in the midst of degenerative or secretory mucin, for example in gelatinous carcinomas, mucinous ovarian adenocystomas, degenerating chondroblastic tumors or Schneiderian cancer with an overproduction of mucous. Secretion, however, is the expression of the assumption of adult character in a tumor cell and hence must supposedly render it more resistant.

13. The anatomic characteristics are of decided importance. Among these may be mentioned the papillary character, delicacy of the blood supply and enclosure within a firm capsule, which may result in the



obliteration of circulation after irradiation has caused the tumor to become edematous. Diffuse lymphatic plugging by tumor cells may lead to edema and interference with cell-fluid exchanges.

14. In the case of certain tumors some unknown physiologic mechanism seems involved in the response to radiation. Examples of this appear in myoma uteri and carcinomas of the breast, ovary and thyroid.

15. The effect of radiation is always complex. It involves not only the tumor cell, but the tissues of the host, and possibly general reactions on the part of the host. The ultimate effect of the radiation must always result from a nice balance between tumor effect and response of the host tissue. The relative importance of the two mechanisms varies in different tumors. In some instances the known sensitivity is such that the radiologist may endeavor to destroy the tumor cells. In others he can but hope for restraint of growth by moderately affecting the tumor cell and trusting that the responses of the host tissue will play a decided rôle. Under such circumstances tumor cells may remain in an indolent state in the midst of fibrous tissue for many years without giving rise to further damage.

16. Unfortunately, more particularly in the case of the extremely sensitive tumors, the radiologist is apt to be so impressed with the initial regression of the disease that he fails to push his treatment to tolerance and waits until, after a period of quiescence, the disease recurs in a more resistant form, when he must essay to do under poorer conditions what he failed to do at the start.

# EXPERIMENTAL CHRONIC ARTHRITIS (SYNOVITIS)

PRODUCED BY INTRA-ARTICULAR INJECTIONS OF BACTERIAL  
FILTRATES AND OTHER FOREIGN PROTEINS

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AND

LUCY DELL HENRY, B.S.

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In recent years the allergic hypothesis for the etiology of chronic arthritis, especially the proliferative type, has received considerable attention.<sup>1</sup> According to this theory, the articular changes are local manifestations of a generalized allergic state. As early as 1902, Menzer<sup>2</sup> suggested that streptococci first gained access to the joints, but that this did not result in inflammatory changes until antibodies were produced. Further researches by Weintraud,<sup>3</sup> Henry,<sup>4</sup> Faber,<sup>5</sup> Friedberger,<sup>6</sup> Freiberg,<sup>7</sup> Klinge<sup>8</sup> and Gudzent<sup>9</sup> demonstrated that arthritic changes could be produced in experimental animals by first sensitizing the animal to bacterial or nonbacterial proteins and then by injecting the antigen into the joints. Similar results were obtained if the antigen was injected first into the joint and later into the general circulation. Swift<sup>10</sup> and his coworkers have recently studied experimental streptococcus allergy

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From the Department of Surgery of the University of Chicago.

1. Brunschwig, A., and Jung, A.: *Arthrites suppurées expérimentales*, *Rev. de chir.*, Paris **50**:521, 1931.
2. Menzer, A.: *Serumbehandlung bei akuten und chronischen Gelenkrheumatismus*, *Ztschr. f. klin. Med.* **47**:109, 1902.
3. Weintraud, W.: *Ueber die Pathogenese des akuten Gelenkrheumatismus*, *Berl. klin. Wchnschr.* **50**:1381, 1913.
4. Henry, Lucy Dell: *Contribution à l'étude du rhumatisme articulaire aigu*, *Bull. Acad. roy. de méd. de Belgique* **28**:76, 1914.
5. Faber, H. K.: *Experimental Arthritis in Rabbits*, *J. Exper. Med.* **22**:615, 1915.
6. Friedberger: *Ueber aseptisch-erzeugte Gelenks-Schwellungen beim Kaninchen*, *Berl. klin. Wchnschr.* **50**:88, 1913.
7. Freiberg, J. A.: *Allergy as a Factor in Production of Proliferative Arthritis*, *Arch. Surg.* **18**:645 (Feb.) 1929.
8. Klinge, F.: *Die Eiweiss Ueberempfindlichkeit (Gewebsanaphylaxie) der Gelenke*, *Beitr. z. path. Anat. u. z. allg. Path.* **23**:185, 1929.
9. Gudzent, F.: *Experimental Production of Articular Rheumatism*, *Berlin Letter, J. A. M. A.* **99**:236 (July 16) 1932.
10. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: *Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci*, *J. A. M. A.* **90**:926 (March 24) 1928.

in rabbits, with the view of explaining the etiology of rheumatic fever in man principally on an allergic basis, with streptococci as the antigen.

The allergic theory, however, leaves much to be explained concerning the etiology of chronic arthritis. And it is a question whether all of the changes ascribed to allergy in this connection are due to this phenomenon or to other factors.

The following series of experiments were performed to determine what direct effect bacterial decomposition and metabolic products may have on the synovia of experimental animals as compared with other proteins of nonbacterial origin. Daily injections of rather large quantities of filtrates were made in order to rule out as much as possible the allergic factor, so that the lesions obtained may be ascribed to a direct effect of the filtrates rather than to an allergic phenomenon. The continued flooding of the field by a large amount of antigen would serve to desensitize the tissues.

#### PROTOCOLS OF EXPERIMENTS

Filtrates of the following organisms were used: *B. subtilis*, *Streptococcus viridans* (a strain isolated from a case of subacute bacterial endocarditis) and a diphtheroid bacillus obtained from a routine bacteriologic examination of urine and not regarded as a pathogen. They were prepared as follows: one hundred cubic centimeters of beef infusion broth was inoculated and placed in the incubator at 37.5 C. (99.5 F.) for seven days. The cultures were then passed through Berkefeld candles (N) and the sterility of the filtrates was controlled before use. The diphtheroid bacillus passed through the candle repeatedly (filtrable form), and therefore this filtrate had to be sterilized in the autoclave.

*Experiment 1.*—This experiment was made to determine whether or not rabbits are naturally sensitive to the filtrates used.

Four rabbits received intracutaneous injections of 1 cc. of the filtrates, sterile broth being used as control. By the end of four days no positive cutaneous reactions had developed.

*Experiment 2.*—This experiment was made to study the effects of unheated *B. subtilis* filtrate and autoclaved *Streptococcus viridans* filtrate on the synovia of rabbits' knee joints after repeated intra-articular injections.

One cubic centimeter of each of the filtrates mentioned was injected into the right and left knee joints, respectively, of rabbits. One animal was killed twenty-four hours after two daily injections; another after seven daily injections, and three after twenty-one injections made over a period of four weeks, no two injections being given less than twenty-four hours apart.

The joints were slightly swollen after the second or third injection, but they did not seem to cause much discomfort to the animals. Grossly, the joints contained a slight mucopurulent exudate after two injections, a more viscous exudate after seven injections and a frankly mucopurulent exudate after twenty-one injections. After seven injections, the synovia was pale yellow and moderately edematous, but after a month of exposure to the filtrates it became markedly swollen, and its color changed to tan; at no time were there ulcerations. All exudates from the joints were cultured and remained sterile after three weeks' incubation. Histologic study of the synovial membranes from the various rabbits revealed that after two injections there were a slight edema and diffuse leukocytic

infiltration with a large percentage of eosinophils. After seven injections the edema and leukocytic invasion were more pronounced. There was still a large percentage of eosinophils and in places small foci of lymphocytes were present in the superficial portions of the synovia. After twenty-one injections made during one month's time, the changes were marked. The synovia was thickened, owing to edema of the deeper portion and a rather extensive fibrosis of the superficial portion, with dense diffuse and focal infiltration by lymphocytes, macrophages and some plasma cells. Some eosinophils were still present, but not in the numbers seen in earlier sections. The synovial villi were thickened, club-shaped and distended by infiltrating leukocytes and proliferation of fibrous tissue.

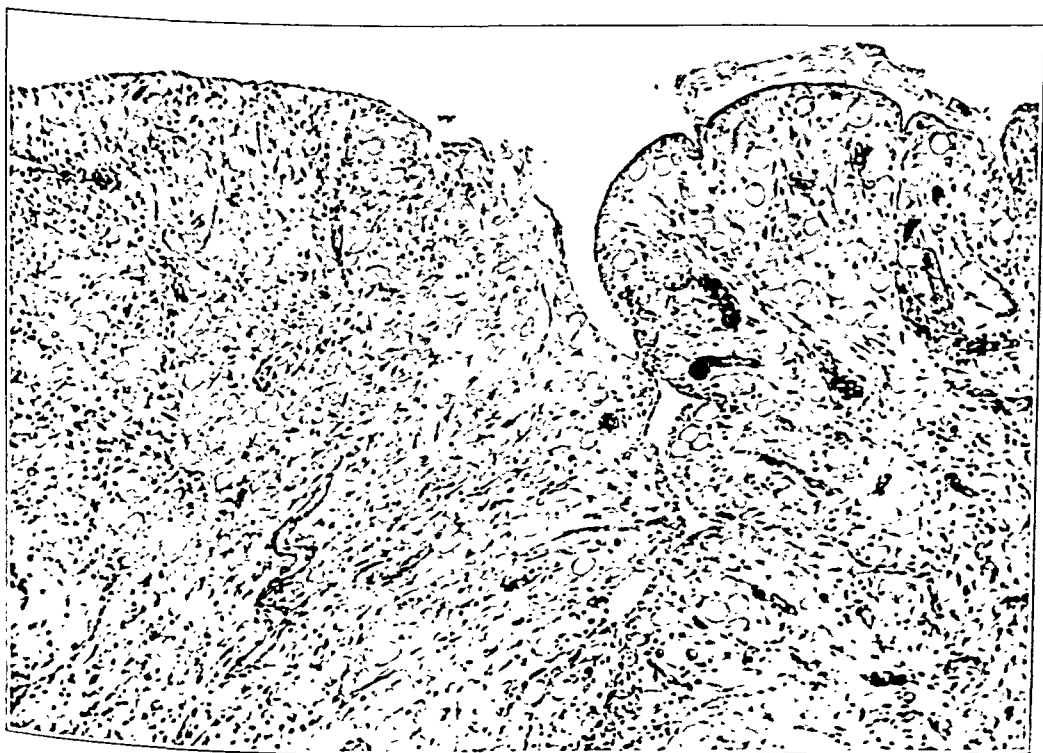


Fig. 1.—Photomicrograph showing synovia from rabbit's knee joint after two daily intra-articular injections of *B. subtilis* filtrate. There are slight edema and diffuse infiltration by leukocytes, mainly eosinophils; reduced from a magnification of  $\times 120$ .

There was no gross evidence of the destruction of cartilage in any of the joints examined, but in those into which injections were made over a period of a month the cartilage was duller than normal.

*Experiment 3.*—Five rabbits were used in this series. Similar injections were made as in the previous experiment, unheated *Streptococcus viridans* filtrate being injected into the right knee and autoclaved *B. subtilis* filtrate was used in the left knee. The rabbits were killed at similar intervals after the same number of injections as previously. The synovia showed changes identical to those just described.

*Experiment 4.*—A third series of three rabbits received intra-articular injections of autoclaved diphtheroid bacillus filtrate in the right knee. One rabbit was killed after two daily injections and two rabbits after twenty-one injections given during a period of one month. The gross and histologic observations were essentially the same as those found in experiment 2.

*Experiment 5.*—An experiment was made to study the effects of intra-articular injections of viable cultures of the organisms the filtrates of which were used in previous experiments.

Into both knees of three rabbits, 1 cc. of a centrifugated seven-day culture of the *Streptococcus viridans*, *B. subtilis* and diphtheroid bacilli used in the previous

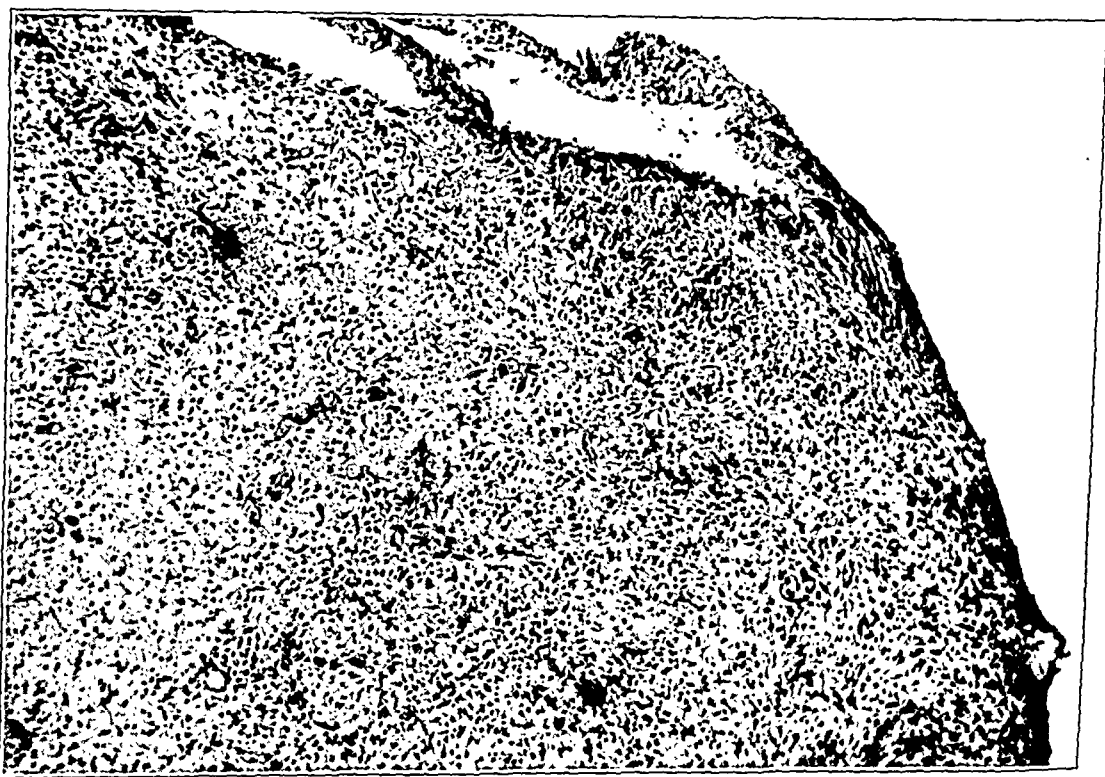


Fig. 2.—Photomicrograph of synovia or rabbit's knee joint after seven daily intra-articular injections of *B. subtilis* filtrate. Moderate edema and moderate infiltration by leukocytes, mainly eosinophils are seen; reduced from a magnification of  $\times 120$ .

experiments were injected respectively. No gross changes were noted in the knee joints. One month after injection the animals were killed. There was no exudate in the joints; cultures of the synovia were sterile. Histologic examination revealed normal synovial membranes. Since the organisms were not able to grow in these animals, sufficient metabolic and decomposition products were not present in the joints to produce synovial changes.

*Experiment 6.*—This experiment was made to study the effects of egg white and human blood serum in the synovia of rabbits. Preliminary intracutaneous injections into two rabbits showed no natural sensitivity to these proteins.

Three rabbits were used in this experiment. Normal human blood serum and egg white, obtained under sterile conditions were diluted with physiologic solution of sodium chloride, in a proportion of 1:10, and intra-articular injections were carried out as in experiment 2. One cubic centimeter of human blood serum was injected into the right knee and a similar quantity of egg white into the left. One animal was killed twenty-four hours after the second daily injection. The synovia was practically unchanged. After twenty-one injections made during a period of one month, the other two animals were killed; cultures of the mucopurulent exudate from the joints were sterile. Sections of the edematous yellowish synovia revealed essentially the same picture of chronic synovitis as was



Fig. 3.—Photomicrograph of synovia of the knee joint after twenty-one intra-articular injections of *Streptococcus viridans* filtrate. There is no ulceration of the synovia; the superficial portions are fibrotic and exhibit diffuse and focal infiltration by leukocytes, mainly lymphocytes. *A* shows section through enlarged synovial villus; reduced from a magnification of  $\times 120$ .

obtained with the bacterial filtrates, except that the leukocytic infiltration was perhaps slightly more diffuse, and that there was a little less fibrosis in the superficial portion of the synovia.

*Experiment 7.*—A control experiment was performed to study the effect of a nonprotein irritant on the synovia.

One cubic centimeter of xylol (an active vesicant) was injected into the right knee joints of two rabbits. On the following and subsequent days the joints were swollen, warm and obviously tender. Because of the severe reaction no other

injections were made. One month later the animals were killed. The capsules of the knee joints had perforated in several places, allowing the thick, purulent exudate from the joints to infiltrate into the periarticular tissues. The synovia was soft, thickened, yellow and easily torn. The articular cartilages were dull, but grossly exhibited no areas of destruction. Sections of the synovia showed extensive edema and diffuse infiltration by all types of leukocytes, with foci of tissue necrosis and ulceration in the synovial lining. The histologic appearance was not that of a gradually developing sclerotic type of chronic inflammation as seen in sections from the synovia of those joints subjected to repeated injections of the bacterial filtrates.

Injections of sterile broth mediums were not made as controls for this series of experiments, since in a previous report Brunschwig and Jung<sup>1</sup> showed that such injections made daily for a period of three weeks produced only slight changes in the synovia. These changes were characterized by slight edema, no fibrosis and very slight diffuse infiltration by leukocytes.

#### COMMENT

The experiments performed demonstrate that bacterial decomposition and metabolic products brought into direct contact with synovia are capable of inciting an acute inflammatory reaction which if kept up evolves into a chronic stage in a short time. There are at first only moderate edema and diffuse leukocytic invasion. This is followed by fibrosis and dense focal accumulation of leukocytes, primarily lymphocytes, in the synovia, with club-shaped enlargement of the villi. An interesting feature is the large number of eosinophils present as infiltrative cells in the more acute stages. In the later chronic stage the number of eosinophils is markedly reduced. There is no difference between the reaction produced by filtrates of *Streptococcus viridans* (a pathogen), by *B. subtilis* (a saprophyte) and by diphtheroid bacilli. The substances in the filtrates capable of inciting this reaction are heat-stable, since they withstand autoclaving for fifteen minutes at 120 C. (248 F.) and 15 pounds (6.8 Kg.) of pressure.

Almost identical inflammatory reactions are produced in the synovia by such foreign proteins as egg white and human blood serum, which of course are not bacterial in origin.

The changes described are considered primarily the result of a direct action of the foreign proteins on the synovia rather than an allergic phenomenon. The histologic appearance of the synovia is not comparable to that of Arthus' phenomena produced in the subcutaneous tissues of rabbits with tuberculin. In the latter there are extensive edema, necrosis and interstitial fibrinous exudation with dense diffuse and focal polymorphonuclear infiltration. In the synovial membranes of the animals used in the experiments described there is at first a relatively mild reaction, which, under continued exposure to the injected substances, becomes more pronounced, exhibiting the histologic picture of a long-standing chronic, sclerosing, nonspecific inflammation.

The eosinophil has long been identified with allergic reactions. It also has been regarded as the cell of defense against soluble toxic substances, in contrast to the polymorphonuclear neutrophil which is so readily mobilized in invasion by particulate matter such as bacteria. Therefore the presence of eosinophils in the earlier stages of the inflammatory reaction produced in the experiments described may not be interpreted as evidence of allergy, but may be accounted for by the soluble nature of the noxious agents used. Eosinophils are not rarely seen in the synovia in proliferative arthritis in man.

A further review of the extensive literature on the allergic hypothesis for the etiology of arthritis is beyond the scope of this paper. An excellent summary of the question has recently been made by Jordan,<sup>11</sup> and the reader is referred to this publication for a more detailed discussion and bibliography.

In conclusion, it may be stated that if changes in the articulations of animals resembling chronic arthritis in man have been produced by causing an allergic reaction to occur in these joints, it has also been possible to produce such lesions by direct action of foreign protein material of either a bacterial or a nonbacterial source.

#### SUMMARY

1. Filtrates of seven day cultures of *Streptococcus viridans*, *B. subtilis*, and a diphtheroid bacillus repeatedly injected at short intervals into the knee joints of rabbits induce first an acute inflammatory reaction characterized by edema and leukocytic infiltration (mainly eosinophils) in the synovia and later by fibrosis and a dense focal and diffuse round cell invasion, with few eosinophils and a club-shaped enlargement of the synovial villi.

2. Similar changes are produced by the injection of egg white and human blood serum.

It is believed that the lesions produced are primarily the result of a direct action of the filtrates and other proteins on the synovia, and that they are not allergic phenomena.

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# SYMPATHETIC SYSTEM AND PAIN PHENOMENA

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Although the somatic nerves are still regarded as the mediators of afferent impulses, there has been an accumulation of evidence to show that the sympathetic system possesses a sensory function and is concerned in the production of certain types of intractable neuralgia.

It is the objective of this paper to outline the conclusions of certain experimental and clinical observations, illustrating the afferent associations of the sympathetic system, and to correlate these facts with the results of sympathectomy for severe neuralgic conditions.

## RESIDUAL SENSATION AFTER SOMATIC DENERVATION

Surgical intervention has shown that in cases of intractable neuralgic crises in which there has been an extensive division of the posterior spinal roots the resultant anesthesia is often incomplete, and the pain has persisted. Foerster's<sup>1</sup> results for the gastric crises of tabes dorsalis were 49 per cent cure and 51 per cent failure or partial relief only. In two of Thorburn's cases, which I<sup>2</sup> examined in some detail, there was complete retention of deep sensation, although there had been a bilateral posterior rhizotomy of the fifth to the eighth roots in one instance and a unilateral posterior rhizotomy of the fifth to the ninth roots in the other. Both were clinical failures. Other surgeons have obtained comparable results.

The presence of deep sensation after section of the somatic sensory roots suggested: (1) experimental irritation in a case of this type with a known sympathetic stimulant; (2) section of the nerve roots in animals to endeavor to elucidate the path of the residual sensation; (3) observations of cases in which anterior rhizotomy had been performed.

*These lines of investigation were carried out; the details are given elsewhere; it will suffice here to state the results.*

1. A case in which posterior rhizotomy had failed to relieve gastric crises was selected. In the area of surface anesthesia the sweat secretory and pilomotor functions were demonstrated, and the sympathetic system was stimulated by the injection of epinephrine. A serious crisis resulted, which began immediately after the administration of the epinephrine, with the onset of pain within the area of surface anesthesia,

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1. Foerster, O.: Surg., Gynec. & Obst. **16**:463, 1913; Proc. Roy. Soc. Med. (Sect. Surg.) **4**:226, 1910-1911.

2. Shaw, R. C.: Brit. J. Surg. **9**:450 and 454, 1922; **11**:648, 1924.

and it was found that there was a marked lowering of the threshold for pressure pain everywhere in this area. This suggested that the sympathetic, the retained deep sensation and the lowered deep sensory thresholds were interrelated.

2. A series of rhizotomies was performed on animals, and it was found, on testing the deep tissues with a pinch-prick stimulus after extensive section of the posterior root, that a certain percentage of cases exhibited evidence of residual sensation.

W. Lehmann<sup>3</sup> of Göttingen, working on the same subject, obtained corroborative evidence in dogs; division of the dorsal roots resulted in anesthesia of the abdominal wall; but there was no loss of sensation in the abdominal viscera or their vascular supply. On the other hand, after division of the corresponding ventral roots only, converse results were obtained.

This work proved that the ventral roots were the mediators of the residual sensation. In my cases staining of the central ends of the severed anterior roots showed evidence of degeneration, thus eliminating the possibility of sensory fibers from the dorsal ganglions entering the spinal cord with the motor outflow.

3. Investigation of a case of Thorburn's, in which there had been division of the anterior and posterior roots for gastric crises, revealed total anesthesia of the body wall and freedom from pain seven years after operation.

Several cases have been reported in which posterior rhizotomy has failed to relieve intractable neuralgia in amputation stumps, but division of the remaining ventral roots has completely abolished the pain syndrome.

The remarkable contraction of the anesthetic area following section of the posterior root of the fifth nerve has long been recognized. Recently Helson and Frazier<sup>4</sup> have shown that after section of the sensory roots of the fifth nerve, along with other evidence of sensory restoration, the subject responds to an extremely hot stimulus, which appreciation is lost if, in addition to the division of the sensory root, a thoracic sympathectomy has been performed.

This evidence shows that the residual sensation after division of the somatic innervation to an area of its body is dependent on fibers that traverse the ventral spinal roots, that the fibers are probably of sympathetic origin and pass through the anatomic sympathetic channels, and that this sensory residue is capable of excitation by chemical stimuli of known sympathetic proclivity. Lastly, after somatic denervation ordinary methods of sensory examination may elicit a response after a suitable period of recovery has elapsed.

3. Lehmann, W.: *Ztschr. f. d. ges. exper. Med.* **12**:331, 1921; *Zentralbl. f. Chir.* **49**:435, 1922.

4. Helson, H., and Frazier, C. H.: *Brain* **55**:114, 1932.

DUAL TYPE OF SENSATION ELICITED BY IRRITATION OF THE  
CERVICOTHORACIC SYMPATHETIC GANGLION

In order to demonstrate the effects of direct irritation of the sympathetic pathway, I carried out a cervicothoracic ganglionectomy by the supraclavicular route under procaine hydrochloride anesthesia of the superficial tissues. The patient was given an injection of morphine and scopolamine at a sufficient interval before the operation to dull his mental acuity during the initial exposure of the ganglion chain. By the time the cervicothoracic ganglion was exposed he was reasonably appreciative of all sensation. I found that light pinching of the upper pole of the ganglion produced a sensation of touch which the patient referred to the region of the axilla, but crushing of the ganglion with artery forceps caused an excruciating pain of a burning and gripping character, which was felt inwardly over the region of the heart. This pain did not follow instantly after the crushing, but began after a latent period of a few seconds, increased in intensity for an appreciable time and, after some minutes, gradually waned and died away. On removal of the ganglion by traction on the thoracic chain, a similar outburst of pain was excited, which lasted about twenty-four hours, but varied considerably in intensity during this period.

Leriche<sup>5</sup> and others have observed the burning and boring character of pain following manipulation of the sympathetic chain, and analogy with Helson and Frazier's observations is at once suggested.

I<sup>6</sup> have discussed elsewhere the presence of a small group of large medullated fibers (from 10 to 13 microns) in the cervical sympathetic chain, which are comparable to the large sensory fibers described by Langley<sup>7</sup> that terminate in capsular end-organs, and also to the large fibers mentioned by Gaskell<sup>8</sup> and by Edgeworth.<sup>9</sup> They are present in the cervicothoracic chain; a few fibers are distributed in the branches to the brachial roots and the vagus nerve, and others ascend the cervical chain to the superior ganglion.

It is probable that the fibers originate from the cells of the posterior spinal ganglia. There is, therefore, in the anatomic sympathetic chain a sensory pathway which may subserve ordinary somatic sensation, and this might explain the ready appreciation of light touch on the ganglion in the case I mentioned. On the other hand, the burning and boring type of pain that was elicited on crushing the ganglion suggests a different origin in view of the latent period of onset, the

5. Leriche, R.: *Ann. Surg.* **74**:385, 1921; **88**:449, 1928.

6. Shaw, R. C.: *Lancet* **1**:640, 1924.

7. Langley, J. N.: *J. Physiol.* **56**:382, 1922; *Tr. Roy. Soc. London, s.B.* **183**: 118, 1892.

8. Gaskell, W. H.: *J. Physiol.* **7**:1, 1886.

9. Edgeworth, F. H.: *J. Physiol.* **13**:260, 1892.

gradual increase of intensity after the cessation of the stimulus and its slow subsidence. Its main characteristics may be compared to the pain produced by the tabetic crisis invoked by the injection of epinephrine, and seems to be definitely associated with the sympathetic fibers.

Pathologic irritation of the anatomic sympathetic pathway may therefore stimulate both types of pain, resulting in a composite form of neuralgia.

#### RELATION BETWEEN THE SYMPATHETIC SYSTEM AND SOMATIC SENSORY PERCEPTION

I have cited a case in which it was observed that during an epinephrine-produced crisis there was a marked lowering of the threshold for deep pressure in the area of pain, that is, within the area of somatic anesthesia, following posterior rhizotomy. This suggested that variations in the threshold for pressure pain might be produced through the medium of the sympathetic system.

In 1924, I<sup>10</sup> showed that the stimulation of a mixed nerve, such as the median, with a faradic current produced variations in the threshold for pressure pain. It was found that: 1. Weak faradic stimulation of the median nerve caused a marked lowering of the threshold in both cutaneous and deep receptors; this was accompanied by vasodilatation. 2. Strong faradic stimulation raised the threshold in both cutaneous and deep receptors; this was accompanied by vasoconstriction. 3. The same changes occurred even if the circulation had been excluded for from five to eight minutes; therefore, the vascular change cannot be held to explain the sensory variation.

When these experiments were repeated recently, it was found that obstruction of the circulation caused a prolongation of the recovery period, suggesting that the assumption of a certain sensory phase is associated with the liberation of metabolites in the tissue spaces, which affect the sensory receptors. The next step was to estimate the threshold for pressure pain before and after periarterial sympathectomy and ganglionectomy. It was found, in a series of cases, that removal of the sympathetic supply produces a definite fall in the thresholds, and that after the periarterial operation the minimum sensory phase may persist for two or three weeks; after ganglionectomy it may be extended for a few weeks longer.

Claude Bernard<sup>11</sup> observed this exaltation of sensation after sympathectomy, and recently Auguste Tournay<sup>12</sup> described experiments on animals illustrating it.

10. Shaw, R. C.: *J. Physiol.* **58**:288. 1924.

11. Bernard, Claude: *Leçons sur la physiologie et la pathologie du système nerveux*, Paris, J. B. Baillière, 1858, vol. 1, p. 20.

12. Tournay, A.: *Compt. rend. Acad. d. sc.* **173**:939 (Nov. 14) 1921.

The relationship, therefore, between the sympathetic and the somatic sensory apparatus would appear to be that of a brake or control of the sensory thresholds, and its loss causes a temporary fall below the normal threshold value.

It is conceivable that this function would be called into play in the fright-fight syndrome, the healing of wounds and sexual function. Further, this relationship emphasizes the remarkable dissociation between the sympathetic pain syndrome of certain neuralgias and somatic sensation.

#### SURGICAL EVIDENCE OF THE SYMPATHETIC PAIN PATH

Surgical procedures have been carried out for a variety of conditions of pain, both visceral and peripheral, and many successful cases have been reported. In reasoning from such material that a specific pain pathway has been severed by the operation, one is open to fallacy if one considers the relief of the symptoms from another standpoint. It is obvious that if an area of tissue, for example a finger, is undergoing necrotic change the chemical products of disintegration might irritate the sensory endings, and the arrest of the degenerative process by vasodilatation might give an equivalent relief from neural irritation progressive in character and tending to final cure.

In order that it may be reasonably inferred that the operation of sympathectomy definitely removes or interferes with the mechanism of the pain apparatus, cases should fulfil the following conditions: 1. There should be severe preoperative pain and immediate postoperative relief. 2. There should be an absence of a gross pathologic lesion, the healing of which might account for the subsidence of pain, or, conversely, if such a lesion exists, the pain should cease long before it heals. 3. There should be an absence of pain in cases exhibiting a minimum degree of postoperative thermal response, showing that the relief from pain is not entirely due to the secondary benefits of increased metabolic activity.

The following cases have fulfilled these requirements, and may be considered in two groups, according to whether the paraspinal ganglion or the periarterial plexus was removed.

#### REPORT OF CASES

CASE 1.—*History*.—A. G. F., a man, aged 42, a fitter, had had severe pain in the left thigh in 1928; the pain steadily became worse, and flexion deformity of the left hip joint developed. In 1929, he was admitted to the infirmary and treated with massage and electricity; the pain remained severe; wasting of the muscles began, and he rapidly became emaciated.

The patient was readmitted to the infirmary on May 5, 1931, complaining of severe pain over the left thigh, radiating to the foot; the pain was of a burning

and boring character, and was accompanied by profuse sweating and marked vasoconstriction. He was extremely emaciated; there was advanced osteo-arthritis of the left hip joint; the thigh was held in a position of 60 degrees of flexion. There were marked tenderness and pressure over the left foot. There was no tenderness of the sciatic nerve.

*Operation and Course.*—On August 1, left lumbar ganglionectomy was performed, with the removal of the second, third and fourth lumbar ganglions.

The pain ceased immediately after the operation, except for local pain on movement of the hip joint; the leg became warm and dry, having a rise in surface temperature of 6 C. (42.8 F.); further treatment of the hip joint was refused, and the patient was discharged.

Reexamination on Feb. 1, 1933, showed the patient still entirely free from crises of pain, and he had gained weight; his osteo-arthritic condition had progressed; the leg was still warm and dry.

*CASE 2.—History.*—P. McC., aged 54, an ex-soldier, several weeks prior to admission, had severe crises of pain in the index finger of the left hand; the pain radiated up the arm; it was continuous day and night, and he lost sleep; discoloration and terminal necrosis of the distal phalanx began. He was admitted to the hospital on June 16, 1931, with a bluish discoloration of the whole index finger of the left hand, with necrosis of the superficial layers of the terminal phalanx; the pain was of a severe, burning, aching character, with critical exacerbation and radiation up the arm.

*Operation and Course.*—On June 16, excision of the left cervicothoracic and middle cervical ganglions was performed under procaine hydrochloride anesthesia.

After twenty-four hours all pain ceased in the left arm and hand; the bluish discoloration rapidly subsided, and the necrotic area of the left index finger was slowly desquamated. The surface temperature showed an average rise of only 1 F. on the left hand.

On Oct. 15, 1932, reexamination showed that the left hand had remained entirely free from pain, and there was no evidence of any further necrosis of the fingers. A new nail had grown on the left index finger. The surface temperature of the left midpalm was 0.5 F. higher than that of the right, and the surface temperature of the left index finger was 1 F. higher than that of the right. On exposure to cold, both hands showed a bluish discoloration.

*CASE 3.—History.*—W. L. H., a man, aged 29, an iron worker, had a condition which began three years prior to admission with a perforating ulcer on the plantar aspect of the right great toe, which was said to have followed irritation with a nail in a boot.

On admission, the whole surface of the great toe and the dorsum of the foot showed a bluish-red discoloration. On the plantar aspect of the great toe was a soft, punched-out ulcer 1 inch (2.5 cm.) in diameter; the edge was ragged; the base was indurated, and the floor showed a sloughing area. The patient complained of a severe burning and aching pain over the dorsum of the foot from the great toe to the ankle joint and radiating to the knee; the pain was continuous, but showed critical exacerbation.

Examination of the nervous system revealed nothing abnormal. The general condition was excellent.

*Operation and Course.*—On Sept. 12, 1932, a proprietary procaine preparation was injected, and the surface temperature showed a rise of approximately 8 F.; a right lumbar ganglionectomy was performed, the second, third and fourth ganglions being removed.

The pain ceased immediately after operation. The bluish-red discoloration had disappeared by the third day, and the ulcer rapidly contracted in the area and dried up, showing a keratinized surface. An estimation of the surface temperature after operation gave an average rise of 2 F. on the right foot compared with the left.

Reexamination six weeks after operation showed no recurrence of pain. The surface temperature of the right foot still showed a rise of 2 F. above the left foot.

Three cases have been described in which there was severe pain up to the time of operation, and after extirpation of the sympathetic fibers the relief was practically immediate.

In the first case, there was no gross pathologic lesion of the surface of the limb which might account for the pain, and the condition must have been due to a pure irritation of the sympathetic pathway, which ceased on its removal. The pain could have borne no relationship to the chronic and slowly progressive osteo-arthritis of the hip joint.

In the other cases a distal surface lesion existed, but the pain ceased directly after operation and, therefore, long prior to the final desquamation and healing of the necrotic foci.

Finally, the thermal response in all of the cases was of a minor degree, yet, despite the small difference in temperature, the pain syndrome was promptly abolished, discounting the view that the relief from pain is due to improved metabolism.

It is from the minor periarterial operation that one obtains secondary evidence that the continuity of the sympathetic neural apparatus is intimately concerned in the maintenance of many neuralgic conditions. The following three cases showed immediate relief from severe pain crises after stripping of the perifemoral adventitial sheath and the injection of absolute alcohol into the severed extremities of the plexus.

*CASE 4.—History.*—On Sept. 9, 1930, a man, aged 56, a fireman, complained of a small ulcer over the plantar surface of the hallus of the right foot. It became extremely painful and gradually extended, being surrounded by an edematous, tender, dusky red area. Finally, the great toe became completely black. A fortnight prior to admission the same process began in the second and third toes of the same foot.

On admission to the hospital on December 20, examination showed that the patient was suffering from a severe pain in the medial three toes of the right foot. There was a deep sloughing ulcer over the plantar surface of the great toe, and the second and third toes showed definite gangrene. The remaining toes were deeply cyanotic, and there were redness and slight edema on the dorsum of the foot.

*Operation and Course.*—Right perifemoral sympathectomy was performed on December 20.

The ulcer on the great toe slowly dried up after the removal of a small scab; the toe became completely healed. The gangrenous second and third toes speedily showed a line of demarcation, and were later disarticulated. The pain

disappeared within the first twenty-four hours, and the cyanosis subsided within a week. The average postoperative rise in surface temperature was 1 F.

On July 7, 1931, examination showed that the foot was soundly healed and free from any painful sensations.

On reexamination on Oct. 15, 1932, it was found that pain had been returning in the foot during the past three weeks. There was no further necrosis. The surface temperature increased from 0.5 to 1 F.

*CASE 5.—History.*—A man, aged 47, a night watchman, had complained of a sore spot on the plantar surface of the fourth toe for two weeks prior to admission. The three lateral toes had been extremely painful. The pain, which was of a burning, boring character, had started two months previously.

On admission to the hospital, the entire right foot was extremely painful and of a dusky red hue. There was a black discoloration of the two lateral toes, and slight discoloration of the third toe, which was extremely tender to pressure. There was a slight edema over the dorsum of the foot.

*Operation and Course.*—Right perifemoral sympathectomy was performed on May 5, 1931.

The pain subsided immediately after operation; the discoloration of the toes disappeared within a fortnight, with the exception of a small area of the extremity of the fourth toe, which became mummified and separated from the normal tissues. The surface temperature rose from 0.5 to 1 F.

This patient remained free from pain for six months, when he died suddenly.

*CASE 6.—History.*—A woman, aged 66, a housewife, stated that her right foot had been injured by a nail five months prior to admission; a severe burning and boring pain had begun in the foot, and had become much worse during the last month. An area of necrosis appeared at the base of the small toe, and another area on the ball of the great toe.

On admission to the hospital on June 13, the pain was extremely severe.

*Operation and Course.*—Perifemoral sympathectomy was performed on June 6.

The pain ceased immediately after operation, and the patient was free from pain on reexamination twelve months later. The necrotic area dried up and was exfoliated a few months after operation. The rise in surface temperature after sympathectomy was never more than 1 F.

In the foregoing cases the thermal reactions were almost negligible, but the readings of the pressure pain showed a definite lowering of the distal threshold levels, proving that the proximal operation had affected the extremities of the limb, despite a minimum vascular relaxation.

These results may be compared with those reported by Rogers,<sup>13</sup> of Soonchun, in seven cases of thrombo-angiitis obliterans in which the patients were treated by the injection of alcohol into the perifemoral sheath. He found that all of the patients experienced prompt relief from pain, and the most striking evidence contributory to the present thesis is afforded by one of the cases in which pain and cyanosis of two fingers developed, in addition to a lesion of the foot. In this instance the injection of alcohol into the brachial artery, though it was fibrosed, nonpulsatile and cordlike, resulted in the immediate relief of pain in the hand.

13. Rogers, J. M.: *China M. J.* 45:515, 1931.



The condition of thermalgia provides similar evidence that both the local operative procedure directed at the lesion of a mixed nerve and periarterial sympathectomy have yielded relief from pain. For example, the Russian surgeons, according to Roubacheff,<sup>14</sup> in a series of twenty-nine cases obtained sixteen cures and in twelve instances the patients were definitely relieved by periarterial sympathectomy. Similarly, patients with radiodermatitis have been treated by periarterial sympathectomy, and a reasonable percentage have been relieved from pain.

On account of the anatomic distribution of nerves to the blood vessels, periarterial sympathectomy cannot affect the principal vasomotor supply of a limb nor interfere with the somatic innervation, yet there is evidence from clinical results, thermal reactions and changes in pressure pain that it does produce distal effects in the limb. The explanation seems to lie in the conception of the sympathetic nervous system as a closed neural circuit through the median of the continuous plexus on the vascular tree distributed intimately to all the peripheral tissues. Disruption of this plexus would result in a molecular disturbance radiating through the entire sympathetic plexus, thereby inhibiting the radiation of pain stimuli.

#### CONCLUSIONS

1. The sympathetic fibers may conduct afferent stimuli-subserving common sensation after the extirpation of the somatic innervation; this function appears to develop gradually after removal of the spinal nerve supply.

2. Sympathetic fibers convey impulses of pain in certain types of intractable neuralgia which are distinct from the conditions of pain conveyed by the spinal system.

3. The sympathetic system acts as a control on the somatic sensory thresholds, and the removal of this influence is followed by a temporary increase of common sensitivity.

4. The anatomic sympathetic pathway in the cervicothoracic region contains spinal sensory fibers, the irritation of which might result in a composite type of neuralgic pain.

5. Surgical ablation of the paraspinal ganglions will definitely cure the sympathetic type of intractable neuralgia through removal of the mechanism of pain. Periarterial sympathectomy will certainly relieve pain in similar conditions, and it is suggested that the operation produces its results by the induction of an inhibitory phase through the radiation of molecular shock throughout the sympathetic neural circuit.

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14. Roubacheff, S.: *Rev. de chir.* 65:341, 1927.

# ABSORPTION IN INTESTINAL OBSTRUCTION

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An attempt to ascertain the cause of death in intestinal obstruction immediately gives rise to these fundamental questions: First (the long debated question), are there formation and absorption of a toxin in the loop of the bowel above the obstruction? Second, is there an altered absorption rate, either an increased absorption of substances normally present in the intestinal tract or a decreased absorption below the obstruction because substances secreted in the upper segment fail to reach the lower absorption area? The latter phenomenon may be the fundamental principle of a normal physiochemical balance.

It is now the opinion of most writers and authorities on the subject that intestinal obstruction may be classified either as simple obstruction or as obstruction with gangrene, or interference with the blood supply. We know there is a gross difference between the two conditions. That there is a toxic element in the second group is indisputable; at present the evidence indicates that a definite toxin is not the exciting cause of death in simple obstructions.

In early experiments on this subject, great emphasis was placed on the presence of a newly formed and exceedingly toxic substance in the fluid contents above the obstruction and the fact that absorption was augmented by increased pressure and by changes in the mucous membrane. According to Cooper,<sup>1</sup> Amussat, in 1838, was the first to suggest the existence of toxic absorption. The same theory was widely sponsored by Bouchard in 1885. Since then a great many investigators have attempted to prove that death is caused by a toxin absorbed above the obstructed level, in combination with a disturbance of the acid-base equilibrium. Albeck,<sup>2</sup> Kukula,<sup>3</sup> McClure, Stone, Bernheim and Whip-

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1. Cooper, H. S. F.: The Cause of Death in High Obstruction. *Arch. Surg.* **17**:918 (Dec.) 1928.

2. Albeck, V.: Experimentelle und klinische Untersuchungen über die Todesursache bei Dünndarmstrangulation. *Arch. f. klin. Chir.* **45**:569, 1902.

3. Kukula, O.: Untersuchungen über Autointoxication bei Darmocclusionen. *Arch. f. klin. Chir.* **63**:773, 1901.

ple,<sup>4</sup> Clairmont and Ranzi,<sup>5</sup> and Roger and Garnier<sup>6</sup> believed that they were able to show that a strong toxic factor is at work.

Although Kukula, in 1901, and Magnus-Elsleben,<sup>7</sup> in 1906, had concluded from their experiments that the contents of the bowel both of normal dogs and of those with obstructed intestines were toxic, it was not until Wangensteen,<sup>8</sup> in 1928, substantiated the work of Roger and Garnier and offered further evidence of the toxicity of the contents of the normal intestine that the matter was given serious attention, and it was thought that perhaps the absorption of a specific newly-formed toxin was not the etiologic factor. Wangensteen, after careful experiments, not only established the fact that there was equal toxicity of the contents of normal and of obstructed intestines, but stated that apparently the contents below the obstruction were even more toxic than those above it. The questions of the rate of absorption or the selectivity from above or below the obstruction were not considered in these experiments, and these omissions encouraged us to proceed with a group of experiments on which we had been working for more than a year.

It seems logical that if no specific toxin is present in obstructed loops free from gangrene, the lethal factor must be, as stated in the first paragraph, either increased absorption of substances normally present in the intestine or the failure of a neutralization process or buffer reaction which would ordinarily occur when the contents of the upper and lower intestines mingle. It is also possible that this failure may affect the function of the secretion of the intestinal mucosa and in some remote manner play a rôle in the cause of death.

In 1904, Clairmont and Ranzi presented the first experiments on decreased absorption above obstruction in the intestine, but their results were not conclusive. They injected a 2 per cent solution of calcium iodide into the intestinal lumens of both normal animals and those with obstructed intestines. The urine was then tested at frequent intervals to ascertain the presence of iodine. After numerous experiments, they concluded that the rate of absorption above the obstruction was greater

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4. Stone, H. B.; Bernheim, B. M., and Whipple, G. K.: *Intestinal Obstruction: A Study of the Toxic Factors*, Bull. Johns Hopkins Hosp. **23**:159, 1912. Stone, H. B., and Firor, W. M.: *Absorption in Intestinal Obstruction: Intraintestinal Pressure as a Factor*, Tr. South. Surg. & Gynec. A. **37**:173, 1924.

5. Clairmont, P., and Ranzi, E.: *Zur Frage der Autointoxication bei Ileus*, Arch. f. klin. Chir. **73**:696, 1904.

6. Roger, H., and Garnier, M.: *Compt. rend. Soc. de biol.* **59**:388, 673 and 677, 1905.

7. Magnus-Elsleben, Ernst: *Ueber die Giftigkeit des normalen Darminhalts*, Beitr. z. chem. Physiol. u. Path. **6**:503, 1906.

8. Wangensteen, O. H., and Chunn, S. S.: *Studies in Intestinal Obstruction*, Arch. Surg. **16**:606 (Feb.) 1928. Wangensteen, O. H., and Loucks, M.: *Studies in Intestinal Obstruction*, Arch. Surg. **16**:1088 (May) 1928.

than normal during the first few hours, but that, after reaching a peak at about the mid-point of the survival period, it rapidly fell below normal.

In 1908, Braun and Boruttau<sup>9</sup> injected from 1.2 to 3 mg. of strychnine into the intestinal lumens of normal animals and those with obstructed intestines. In the normal animals, cramps began within five and one-half minutes and death occurred after seventeen and one-half minutes. In animals with obstructed intestines, the cramps began within ten to fifteen minutes, and death occurred within seventeen and one-half to thirty-five minutes. They concluded that absorption was somewhat lessened in the obstructed intestine.

In a study of the absorption of 5 per cent solutions of sodium chloride and dextrose in 1911, Enderlen and Hotz<sup>10</sup> were of the opinion that absorption was much decreased in closed loops.

Davis<sup>11</sup> used phenolsulphonphthalein in 1914, directing the dye into the loops of the intestine and recovering it in the urine at intervals. He concluded that absorption was unusually low in closed loops.

These experiments are rather fundamental, but they are not conclusive, as absorption below the obstruction was not considered, and no experiments were done with substances not normally absorbed from the intestinal tract.

Since considerable evidence has been presented to disprove the presence of a specific toxin in the obstructed intestine, if absorption above the obstruction can be shown to be decreased, or at least not increased, there is some evidence that the cause of death is the failure of a neutralization process or buffer reaction to take place as it would normally when the different levels of intestinal contents mingle.

The work of White and Fender,<sup>12</sup> in 1930, indicated conclusively that no toxin was produced in the intestine above the obstruction, and by restoring material which was lost in the vomitus through an ileostomy below the point of obstruction, they were able to keep animals alive for twenty-eight days.

Meyers and Rosenblatt,<sup>13</sup> in 1929, gave human bile to dogs with obstructed intestines through an enterostomy below the obstruction, but

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9. Braun, W., and Boruttau, H.: *Experimental-kritische Untersuchungen über den Ileustod*, Deutsche Ztschr. f. Chir. **96**:544, 1908.

10. Enderlen and Hotz: *Ueber die Resorption bei Ileus und Peritonitis*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**:755, 1911.

11. Davis, D. M.: *Intestinal Obstruction: Formation and Absorption of Toxin*, Bull. Johns Hopkins Hosp. **25**:33, 1914.

12. White, J. C., and Fender, F. A.: *The Cause of Death in Uncomplicated High Intestinal Obstruction*, Arch. Surg. **20**:897 (June) 1930.

13. Meyers, M. P., and Rosenblatt, M. S.: *Bile in Intestinal Obstruction*, Surg., Gynec. & Obst. **49**:473, 1929.

none of their animals lived long enough to prove that bile was of any particular value. In 1932, Benedict, Stewart and Cutner<sup>14</sup> attempted to evaluate the rôle of bile in high intestinal obstruction. They either injected dog's bile or, by ligating the common bile duct and performing a cholecystenterostomy below the obstruction, permitted the dog to supply its own bile. Some of their animals lived as long as fifty-six days, and they concluded that benefit was derived from the administration of bile below the obstruction, particularly in high obstructions. The conflicting results of these two groups of authors leave one somewhat in doubt as to the importance of bile in intestinal obstruction. However, it would seem that bile alone would not play as important a rôle as the combination of biliary, pancreatic and duodenal secretions. Jenkins,<sup>15</sup> in 1929, attempted to ascertain the rôle of these combined secretions by a complicated operative procedure which permitted the secretions to enter the bowel below the point of obstruction. His animals lived from twelve to thirty-three days.

These experiments suggest that the intermixture of upper and lower intestinal contents is necessary, at least in part, for a normal physiochemical balance. However, they neither support nor deny the factor of an interference with the rate of absorption above or below an obstruction.

In view of the fact that certain authors, after reliable experiments, still cling to the theory of increased absorption either of a specific toxin or of normal intestinal contents above the point of obstruction, the following experiments were carried out in the hope that definite conclusions could be drawn as to the rate and selectivity of absorption above and below an obstruction.

#### ORIGINAL EXPERIMENTS

*Group 1.*—In this group, trypan blue and red, both typical colloids not normally absorbed, were injected into the intestinal lumens of normal rats and into the intestines of rats with obstructions of the duodenum and of the ileum.

In the shorter series of this group, the dye was instilled either by inserting a catheter into the stomach and intestine or by injecting the solution directly into the area above the obstruction with a fine needle. Soon after this was done, the bladders were opened and the urine was examined for the presence of the dye. In no instance was the dye recovered from the bladder.

In the longer series, both normal rats and rats with obstructed intestines were given trypan blue for several days, by means of inserting a catheter into the stomach. Frequent observations were made for the discoloration of the skin, and at the end of from twenty-four to forty-eight hours the bladders were opened and the urine was examined. There was no evidence of the dye, an indication that

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14. Benedict, E. B.; Stewart, C. P., and Cutner, P. M.: *The Rôle of Bile in High Intestinal Obstruction*, Surg., Gynec. & Obst. **54**:605 (April) 1932.

15. Jenkins, H. P.: *Experimental Ileus*, Arch. Surg. **19**:1072 (Dec.) 1929.

new avenues for the absorption of these colloids had not been opened in the obstructed intestine.

In a third series, trypan blue and red were injected below the level of obstruction in both the duodenum and the ileum. There was no evidence of absorption below the obstruction.

*Group 2.*—Methylene blue (methylthionine chloride), a typical crystalloid dye known to have been recovered from the urine after its absorption from the intestines, was used in this group. The first few experiments we carried out on rats to reassure ourselves of the dye's absorption, and then the experiment was carried out on dogs.

Methylene blue was instilled into the duodenum of four dogs of a control group. In the male dogs, the bladders were opened; in the females, a catheter was inserted into the urethra. Urine was collected every five minutes and examined for blue discoloration. The time of its appearance varied between thirty and sixty minutes. The same concentration and amount of dye were used in all animals, but a slight difference in the size of the animals and small variations in time must be taken into consideration.

The intestines of two dogs of about equal size were then obstructed at the duodenum, and those of two others were obstructed near the terminal ileum. On the second or third postoperative day, the abdomens were opened and methylene blue was injected into the lumens above the obstruction. The bladders were opened and observation was made as to the time of the appearance of discoloration in the urine. The time varied between forty-five to sixty-five minutes.

The intestines of two dogs were then obstructed at the duodenum, and in two or three days methylene blue was injected below the obstruction. The dye appeared in the urine in from fifty to seventy minutes.

#### COMMENT

An analysis of the protocols of the second group of experiments showed that there was only a slight variation in time, which could be accounted for by the difference in the size of the animals and particularly by the variations in the amount of retained secretions above the obstruction. Naturally these animals could not be prevented from vomiting, and there could be no control of the biliary, pancreatic and duodenal secretions. An animal with a smaller amount of intestinal contents above the obstruction would have a greater concentration of the dye, and absorption would probably be more rapid than in an animal with greater retention. In no case was the absorption more rapid above the obstruction than it was in the normal dog. When the dye was injected into the lumen below the level of the duodenal or ileal obstructions, the time of its appearance in the urine varied between fifty and seventy minutes, showing that there was no increase and only a slight decrease in absorption below the level of obstruction.

We were unable to demonstrate any increase in the rate or selectivity of absorption above or below the level of obstruction. If one accepts the work of Wangenstein and his predecessors, who believe that normal intestinal contents are as toxic as those above and

below an obstruction, it may be assumed that there is no specific toxin which develops after the onset of obstruction. Our experiments suggest that there is no increase in the rate or selectivity of absorption above the obstruction, and this seems strong evidence that increased absorption above the obstruction cannot be the cause of death. Our experiments also tend to rule out the probability of increased absorption below the obstruction.

With these negative facts in mind, we believe that it is within the realm of probability that death following intestinal obstruction is due to a failure of neutralization or buffer reaction to take place between upper and lower intestinal contents in the lower part of the intestine. This need not be interpreted in terms of the development of a definite toxin, but rather of a physiochemical reaction that usually takes place when the contents of the upper and lower parts of the intestines are permitted to intermix. With this phenomenon there occurs absorption or failure of absorption of a substance,  $x$ , which causes a disturbance not in accord with normal cellular function and incompatible with life. Clinically, our best evidence of this is the fact that an obstruction of the distal colon is compatible with life for some time. This may be explained by the fact that the intermixture of upper and lower intestinal contents has already occurred above the obstruction and absorption has taken place. If the obstruction occurs above the distal colon, in the more active secreting levels and the absorption area, death occurs earlier than in the case of a lower obstruction. Thus, in a subject with an ileostomy, partial admixture and absorption have already taken place; but with complete duodenostomy or jejunostomy, this admixture and absorption have not taken place and death occurs much earlier in the latter than in the former condition.

# PRIMARY MALIGNANT DISEASE OF THE DUODENUM

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Since the first case reported by Hamberger<sup>1</sup> in 1746, the rarity of primary duodenal malignancy has been so stressed that rarely do textbooks mention it, clinicians consider it or surgeons encounter it with a thorough knowledge of the best methods to adopt when this condition unexpectedly presents itself at laparotomy. Therefore, the purposes of this paper are to present a rather thorough summary of the literature on the subject, to emphasize the consideration of a primary malignant disease of the duodenum in the differential diagnosis of lesions of the upper part of the abdomen, to outline the various methods of treating patients with this disease and to add 2 cases to the few that have been reported.

## INCIDENCE

In order that the rarity of primary carcinoma of the duodenum be better appreciated, it might be well to consider first the incidence of intestinal and small intestinal carcinoma as shown in table 1, and then to determine the frequency of small intestinal carcinoma among cases of general intestinal carcinoma by referring to table 2.

Table 3 shows the incidence of primary carcinoma of the duodenum in 350,286 autopsies to be 0.033 per cent. This is the figure most generally accepted in the literature. Difficulty arises in obtaining accurate statistics because of repetition of the same cases by different authors. I have attempted to avoid this by searching the various original sources so far as possible. It is interesting to note that in a series of 17,652 autopsies at Guy's Hospital, as reported by Perry and Shaw,<sup>2</sup> there were 6 cases of primary sarcoma of the duodenum, making its incidence the same as that of carcinoma, namely, 0.033 per cent, which is higher than is generally supposed.

Table 4 illustrates the frequency with which primary carcinoma of the duodenum occurs in comparison with that of the jejunum and ileum combined, and that the duodenum is affected in approximately 45 per cent of the cases of primary carcinoma of the small intestine.

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From the Cleveland Clinic.

1. Hamberger, G. E.: *De ruptura intestini duodeni*, Jena, lit. Ritterianis, 1746.

2. Perry, E. C., and Shaw, L. C.: *On Diseases of the Duodenum*, Guy's Hosp. Rep. 50:171, 1893.



TABLE 1.—*Frequency of Intestinal and Small Intestinal Carcinoma Among General Autopsies*

Author	Autopsies	Intestinal Carcinoma		Small Intestinal Carcinoma	
		Number	Per Cent	Number	Per Cent
Brill; <sup>3</sup> Aaron, <sup>7</sup> Pathological Institute, Vienna .....	41,838	343	0.8	17	0.040
Meyer and Rosenberg, <sup>9</sup> Cook County and Michael Reese Hospitals, Chicago....	10,876	569	5.1	10	0.091
Total.....	52,714	912	1.7	27	0.051

TABLE 2.—*Frequency of Small Intestinal Carcinoma Among General Intestinal Carcinoma*

Author	Intestinal Carcinoma	Small Intestinal Carcinoma	
		Number	Per Cent
Jefferson <sup>14</sup> .....	4,177	130	3.1
Brill <sup>3</sup> .....	3,568	89	2.5
Meyer and Rosenberg <sup>9</sup> .....	569	10	1.7
Aaron <sup>7</sup> .....	343	17	4.9
Total.....	8,652	246	2.7

TABLE 3.—*Frequency of Primary Duodenal Carcinoma in General Autopsies*

Author	Autopsies	Duodenal Carcinoma	
		Number	Per Cent
Deaver and Raydin; <sup>5</sup> McGuire and Cornish <sup>11</sup> .....	151,201	50	0.033
Jefferson <sup>14</sup> .....	109,201	43	0.039
Brill; <sup>3</sup> Aaron; <sup>7</sup> pathological Institute, Vienna.....	41,838	7	0.016
Fenwick and Fenwick (Cancer and Other Tumours of the Stomach, London, J. & A. Churchill, 1902; quoted by Vickers: Ann. Surg. <b>79</b> : 239, 1924); London Hospital....	19,518	18	0.090
Perry and Shaw; <sup>2</sup> Guy's Hospital, London.....	17,652	4	0.023
Meyer and Rosenberg; <sup>9</sup> Cook County and Michael Reese Hospitals, Chicago .....	10,876	4	0.037
Total.....	350,286	126	0.035

TABLE 4.—*Frequency of Primary Duodenal Carcinoma Compared with Primary Jejunio-Ileal Carcinoma*

Author	Small Intestinal Carcinoma	Duodenal		Jejunio-Ileal	
		Number	Per Cent	Number	Per Cent
Deaver and Raydin <sup>5</sup> .....	132	63	47.7	69	52.2
Mayo Clinic <sup>4</sup> .....	39	15	38.4	24	61.5
Brill <sup>3</sup> .....	39	15	59.0	15	50.0
Aaron <sup>7</sup> .....	17	7	41.1	10	58.8
Meyer and Rosenberg <sup>9</sup> .....	10	4	40.0	6	60.0
Total.....	228	104	45.6	124	54.3

This shows that the duodenum is the site of a malignant process almost as frequently as the other two divisions of the small intestine combined. According to some reports the ileum is involved almost as frequently as is the duodenum. Opinions regarding primary carcinoma of the jejunum vary, from that it is practically nonexistent (Brill,<sup>3</sup> 1904) to that it is of equal frequency with carcinoma of the duodenum (Mayo Clinic,<sup>4</sup> 1925).

Table 5 shows that of the anatomic divisions of the duodenum, the second portion undergoes malignant degeneration far more frequently than the other parts. According to Deaver and Ravdin,<sup>5</sup> Brill<sup>3</sup> and others, this probably is due to the presence of the ampulla of Vater and the occasional separate openings of the pancreatic ducts. How-

TABLE 5.—Distribution of Primary Duodenal Carcinoma

Author	Num- ber of Cases	First Portion		Second Portion		Third Portion		Entire Duodenum	
		Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent
Deaver and Ravdin <sup>5</sup> .....	153	35	22.1	104	65.8	19	12.0	0	0.0
Fenwick and Fenwick (Cancer and Other Tumours of the Stomach, Lon- don, J. & A. Churchill, 1902).....	51	11	21.5	29	56.8	7	13.7	4	7.8
Rolleston <sup>22</sup> .....	40	10	25.0	27	67.5	3	7.5	0	0.0
Mayo Clinic <sup>4</sup> .....	15	6	40.0	6	40.0	3	20.0	0	0.0
Perry and Shaw <sup>2</sup> .....	13	5	38.4	6	46.1	1	7.6	1	7.6
Dewis and Morse <sup>6</sup> .....	12	5	41.6	5	41.6	2	16.6	0	0.0
Whittier <sup>8</sup> .....	12	1	8.3	9	75.0	1	8.3	1	8.3
Meyer and Rosenberg <sup>9</sup> .....	4	0	0.0	3	75.0	1	25.0	0	0.0
Total.....	305	73	23.9	189	61.9	37	12.1	6	1.9

ever, the presence of these structures must be differentiated from the presence of a malignant process in these structures, because the latter must be classified as tumors of the pancreatic and biliary systems and not as true primary tumors of the duodenum. Laxity and difficulty in making this distinction undoubtedly have accounted in part for the high percentage of primary carcinomas reported in this portion of the duodenum. The first portion of the duodenum ranks second in order of frequency, owing, perhaps, to the frequent presence of ulcer in this region. Whether or not carcinoma may arise from a duodenal ulcer is, of course, a much debated question, and will be discussed under

3. Brill, N. E.: Primary Carcinoma of the Duodenum, *Am. J. M. Sc.* **128**: 824, 1904.

4. Eusterman, G. B.; Berkman, D. M., and Swan, T. S.: Primary Carcinoma of the Duodenum: Report of Fifteen Certified Cases. *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1925, vol. 17, p. 75; *Ann. Surg.* **82**:153, 1925.

5. Deaver, J. B., and Ravdin, I. S.: Carcinoma of the Duodenum, *Am. J. M. Sc.* **159**:469, 1920.

etiology. The third portion is the part least frequently involved; only 12 per cent of the total number of duodenal cancers have been in this segment.

The sixth decade of life not only is the average age at which carcinoma of the duodenum appears, as shown by table 6, but represents the period of life in which the majority of cases occur, as shown by the reports of Dewis and Morse<sup>6</sup> and of Eusterman of the Mayo Clinic.<sup>4</sup> Aaron,<sup>7</sup> in 1899, after reviewing the literature, stated that a malignant disease of the duodenum occurs most often after the age of 40, and Dewis and Morse,<sup>6</sup> in 1928, concluded that only a small number of persons under 40 years of age were afflicted with this disease. Whittier,<sup>8</sup> in 1889, reported 1 case in a patient aged 17 and 2 cases which occurred in patients 18 years of age. Perry and Shaw<sup>2</sup> collected 9 cases of primary sarcoma of the duodenum and reported the age extremes as 15 and 63 years, with an average age of 31 years.

TABLE 6.—*Age and Sex Incidence of Primary Duodenal Carcinoma*

Author	Number of Cases	Age Extremes	Average Age	Males		Females	
				Num-ber	Per Cent	Num-ber	Per Cent
Brill <sup>3</sup> .....	64	17-84	52	51	79	13	20
Fenwick <sup>17</sup> .....	51	.....	53	37	72	14	27
Mayo Clinic <sup>4</sup> .....	15	39-70	56	12	80	3	20
Meyer and Rosenberg <sup>9</sup> .....	4	36-60	49	4	100	0	0
Total.....	134	17.84	52	104	77	30	22

The fact that primary carcinoma of the duodenum occurs more frequently in men than in women has never been disputed. In table 6 the proportion is shown to be about 3:1. This ratio varies tremendously, chiefly in reports presenting small groups of cases, as for instance, the 4 cases presented by Meyer and Rosenberg,<sup>9</sup> in which all of the patients were men.

#### ETIOLOGY

Up to the present time no more is known concerning the true cause of malignant disease of the duodenum than of malignant processes in any other part of the body. However, several theories have been mentioned in the literature and therefore are presented here.

6. Dewis, J. W., and Morse, G. W.: Primary Adenocarcinoma of the Duodenum: Report of Twelve Proved Cases; Summary of the Literature, *New England J. Med.* **198**:383, 1928.

7. Aaron, C. D.: Carcinoma of the Duodenum, *Philadelphia M. J.* **3**:280, 1899.

8. Whittier, E. N.: Primary Malignant Disease of the Duodenum, *Tr. A. Am. Physicians* **4**:292, 1889.

9. Meyer, J., and Rosenberg, D. H.: Primary Carcinoma of the Duodenum: Report of Four Cases, with a Review of the Literature, *Arch. Int. Med.* **47**:917 (June) 1931.

In 1914, Mayo<sup>10</sup> stated that "when malignant disease of the small intestine is found it is usually due to a pre-existing lesion such as a degenerating polyp, adenoma or papilloma." Aberrant glands of the stomach have been mentioned as a causative factor by McGuire and Cornish.<sup>11</sup> Schofield<sup>12</sup> and Orth<sup>13</sup> believed that cancer arises from Brunner's glands, and Jefferson<sup>14</sup> admitted that this was possible. Others have mentioned pancreatic rests as a possible site of origin, and Jefferson,<sup>14</sup> in 1916, referred to only 1 case in which he regarded this derivation as authentic. Recently Bookman<sup>15</sup> reported another such case. On the other hand, Bland-Sutton<sup>16</sup> thought that it was "fiction" to consider the possibility of carcinoma arising from Brunner's glands or pancreatic rests. The association of duodenal carcinoma with the presence of gallstones has been mentioned by Fenwick<sup>17</sup> and others, but this is generally thought to be purely coincidental. Perhaps the most debated etiologic theory is that simple duodenal ulcer may give rise to a malignant condition of the duodenum. The opinions of various authors are as follows: After carefully reviewing 30 such cases, including 5 of Nattan-Larrier<sup>18</sup> and 5 of Perry and Shaw,<sup>2</sup> Jefferson<sup>14</sup> concluded that "a certain number of the cases were very doubtful examples of duodenal carcinoma arising from duodenal ulcer, and that a causal relationship between simple ulcer and carcinoma was difficult to establish in the case of the duodenum." According to Lichty,<sup>19</sup> the incidence of carcinoma arising on duodenal ulcer is 1:80, while that of gastric carcinoma developing from gastric ulcer is 1:25. Deaver and Ravdin<sup>5</sup> claimed that the frequency was uncertain. Bland-Sutton<sup>16</sup> reported a case of chronic duodenal ulcer which gave rise to a sarcomatous growth. Dewis and Morse<sup>6</sup> claimed that duodenal carcinoma probably arises independently and that little evidence has been found

10. Mayo, W. J.: The Prophylaxis of Cancer, *Ann. Surg.* **59**:805, 1914.
11. McGuire, E. R., and Cornish, P. G.: Carcinoma of the Duodenum, *Ann. Surg.* **72**:600, 1920.
12. Schofield, J. E.: Carcinoma of the Duodenum, *Brit. J. Surg.* **18**:84, 1930.
13. Orth, J.: *Lehrbuch der speciellen pathologischen Anatomie*, Berlin, A. Hirschwald, 1887, vol. 1, p. 850.
14. Jefferson, G.: Carcinoma of the Suprapapillary Duodenum Casually Associated with Preexisting Simple Ulcer: Report of a Case, and an Appendix of 30 Collected Cases, *Brit. J. Surg.* **4**:209, 1916.
15. Bookman, M. R.: Carcinoma of the Duodenum Originating from Aberrant Pancreatic Cells, *Ann. Surg.* **95**:464, 1932.
16. Bland-Sutton, J.: Cancer of the Duodenum and Small Intestine, *Tr. M. Soc.*, London **38**:1, 1914.
17. Fenwick, W. S.: Primary Carcinoma of the Duodenum, *Edinburgh M. J.* **10**:309, 1901.
18. Nattan-Larrier: Les cancers du duodénum, *Gaz. d. hôp.* **72**:1291, 1899.
19. Lichty, J. A.: Peptic Ulcer and Carcinoma in the Duodenum, *New York State J. Med.* **18**:433, 1918.

that it ever has arisen in preexisting benign duodenal ulcers. Similarly, Schofield,<sup>12</sup> in 1930, advocated that duodenal ulcer has never been proved to be a predisposing cause of duodenal carcinoma. Finally, in 1931, Hinton<sup>20</sup> stated that "clinically one can disregard the possibility of duodenal ulcer ever taking on malignant degeneration."

#### PATHOLOGY

Like malignancy elsewhere in the body, the pathologic classification of primary malignant tumors of the duodenum differs widely. After all, deciding whether or not the condition is malignant is of primary importance, while the type of malignancy is only of secondary importance and merely a matter of opinion. The various points of origin have been previously considered under etiology.

In regard to duodenal carcinomas, by far the most frequent type found is the cylindric cell adenocarcinoma arising from the intestinal mucosa. This type has the greatest tendency to encircle the intestine in the form of a band or a ring, particularly in the supra-ampullary portion, either by practically limiting itself to the mucosa in the form of a papillomatous growth (Brill<sup>3</sup>) or by infiltrating the tissues beneath the mucosa (Aaron<sup>7</sup>). In either case the tendency is to obstruct the lumen of the duodenum. Dewis and Morse<sup>6</sup> divided the cylindric cell carcinomas into the hard, fibrous, scirrhous form, having few cells and abundant stroma, the softer medullary form, having many cells and little stroma, and the colloid form, having mucoid degeneration of the cells. The cells may change from a cylindric to a squamous form, which process has been mentioned by Aaron<sup>7</sup> and Whittier,<sup>8</sup> or to a spheroidal form, which, according to Brill<sup>3</sup> and Head,<sup>21</sup> usually grows as a soft, flat excrescence with elongated, overhanging edges and has a tendency to ulcerate. Furthermore, the cells may resemble pancreatic cells, or, as mentioned by Deaver and Ravdin,<sup>5</sup> the carcinoma may be alveolar in type.

Comparatively few cases of primary sarcoma of the duodenum have been reported, and in these, the round cell type predominated. In contrast to carcinoma, Rolleston<sup>22</sup> showed that even though sarcomas tend to involve the duodenal tract more extensively than carcinomas, obstruction of the duodenal lumen is less likely to occur, because the infiltrated duodenal wall is usually softened by the sarcomatous growth, and therefore tends to dilate.

20. Hinton, J. W.: Does Cancer Ever Arise from Ulcers? *Am. J. M. Sc.* **181**: 843, 1931.

21. Head, G. D.: Primary Carcinoma of the Third Portion of the Duodenum. *Am. J. M. Sc.* **157**:182, 1919.

22. Rolleston, H. D.: Carcinomatous Stricture of the Duodenum. *Lancet* **1**:1121, 1901.

Any of the various types of malignancy mentioned are subject to retrogressive or necrotic changes, such as softening and ulceration, and while this is a common finding in malignant conditions of all parts of the duodenum, it is especially likely to occur in those about the papilla of Vater (Brill<sup>3</sup>). In addition, Deaver and Ravdin<sup>5</sup> and Meyer and Rosenberg<sup>9</sup> are of the opinion that most of the carcinomas of the lower or infra-ampullary portion of the duodenum take the form of broad, flat, ulcerating masses with stenosis.

The most common feature of a malignant tumor of the duodenum is its constant tendency to obstruct the duodenal lumen, and as the obstruction increases, various pathologic changes are produced in the adjacent structures, particularly in the stomach and in the portion of the duodenum above the obstruction. In these parts compensatory thickening and hypertrophy of the muscular coat first occur, and as the obstruction increases, there is dilatation of the walls, with incompetency of the pyloric valve and chronic catarrhal inflammation of the mucous membranes, perhaps with superficial ulceration (Brill<sup>3</sup>). On the other hand, a malignant process arising at or close to the papilla of Vater usually has a tendency to obstruct the biliary and pancreatic ducts long before it has had time to attain sufficient size (Rolleston<sup>22</sup>) to obstruct the duodenal lumen, and, therefore, if exploration is made at this time, usually a small, circumscribed tumor with little or no changes in the stomach or proximal duodenal walls is found. With obstruction of the ampulla, dilatation of the biliary and pancreatic ducts results, with the formation of pancreatic retention cysts and possibly suppurative infection of the biliary and pancreatic systems, with abscess formation and fat necrosis (Deaver and Ravdin<sup>5</sup> and Brill<sup>3</sup>). Ely<sup>23</sup> reported a case in which the dilated gall ducts ruptured, resulting in a perinephritic biliary cyst. The duodenal growth may press on the portal vein sufficiently to cause ascites (Fenwick<sup>17</sup>). Perforation into the general peritoneal cavity is rare, but occasionally a slight leakage causes a local abscess to form, which, in the supra-ampullary portion, according to Fenwick,<sup>17</sup> burrows upward to the diaphragm or points near the umbilicus. In 1925, Morrison and Feldman<sup>24</sup> reported a case of primary scirrhus carcinoma arising in a diverticulum of the first portion of the duodenum, and in 1926 they<sup>25</sup> published the complete autopsy report on this case.

23. Ely, J. S.: Carcinoma of the Duodenum Compressing the Common Bile Duct; Obstructive Jaundice; Rupture of Dilated Gall-Ducts with Resultant Perinephritic Biliary Cyst, *Proc. New York Path. Soc.*, 1894, p. 108.

24. Morrison, T. H., and Feldman, M.: Case of Carcinoma of the Duodenal Diverticulum with Consideration of Duodenal Diverticulosis, *Ann. Clin. Med.* 4:403, 1925.

25. Morrison, T. H., and Feldman, M.: Autopsy Report of a Case of Primary Carcinoma in the Duodenal Diverticulum, *Ann. Clin. Med.* 5:326, 1926.

Metastases, even to the contiguous lymph nodes, are not common, and as a rule occur late in the disease (Brill<sup>3</sup>). In 125 cases collected by Outerbridge,<sup>26</sup> metastasis was present in only 27, or 20 per cent. Similarly, Dewis and Morse<sup>6</sup> reported 12 cases, metastasis being present in only 3, or 25 per cent. The most common sites of metastasis are the pancreas, liver and the contiguous lymph nodes (Herman and von Glahn<sup>27</sup>), but involvement of the lungs, supraclavicular glands, bones, gallbladder and peritoneum has been noted in some instances. The metastatic growths seldom attain any great size, probably because of the rapid course of the disease. According to Fenwick,<sup>17</sup> the growth may establish communication with the gallbladder or the contiguous bowel, or may even produce an external fistula. In 1893, Pye-Smith<sup>28</sup> reported a case in which there were two separate duodenal carcinomatous masses, one encircling the intestine just below the pyloric sphincter, the other, a larger rounded mass, being 3 inches (7.6 cm.) lower in the duodenum, and he concluded that the upper, primary tumor gave rise to the lower mass by direct contact.

#### SYMPTOMS

The symptoms of primary malignant disease of the duodenum usually are discussed according to the three divisions of the duodenum, but after reviewing the literature one is impressed by the large group of symptoms common to all portions of the duodenum affected, and by the comparatively small number of symptoms that tend to differentiate obstruction in one portion of the duodenum from that in another portion. Since the chief symptoms of malignant disease of the duodenum depend on obstruction of the duodenal lumen, they vary more with the rapidity of development and the consistency of the growth than with the location of the growth, except when it arises from or close to the papilla of Vater and causes the symptoms of biliary obstruction which may or may not be accompanied by evidence of intestinal obstruction. With this exception and the presence of bile and pancreatic juice in the vomitus, when the obstruction is distal to the ampulla of Vater, all three portions of the duodenum, when obstructed, produce the same symptoms, and therefore their differentiation will be considered in the discussion of diagnosis.

In contrast to obstruction of the large intestine, causing symptoms referable to the intestines, duodenal obstruction causes symptoms refer-

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26. Outerbridge, G. W.: *Carcinoma of the Papilla of Vater*, *Ann. Surg.* **57**: 402, 1913.

27. Herman, N. B., and Von Glahn, W. C.: *Carcinoma of the Supra-Ampullary Portion of the Duodenum*, *Am. J. M. Sc.* **161**:111, 1921.

28. Pye-Smith, P. H.: *Cancer of the Duodenum*, *Tr. Path. Soc., London* **45**: 63, 1893.

able to the stomach (Aaron<sup>7</sup>). In the beginning these symptoms are loss of appetite, gas formation with a feeling of fulness in the upper part of the abdomen, belching and occasional nausea after meals. As the obstruction increases, all of these symptoms are more pronounced, and then vomiting begins, accompanied by constipation, loss of weight and strength, dehydration and various degrees of pain in the upper part of the abdomen. As the degree of obstruction varies from time to time because of ulceration and sloughing of the growth, so do the symptoms vary, thereby occasionally giving rise to periods of relief and improvement.

Vomiting is a common symptom, but may be entirely absent, may cease after a time, or may make its first appearance late in the course of the disease, depending on the type of obstruction. It may occur shortly after each meal, only once a day, or may be recurrent. The vomitus may be small or large in amount, and may be red-streaked, diffusely red, brown, black, yellow or green. Rarely does extensive hemorrhage occur, but coffee ground vomitus is not uncommon.

Pain is a variable symptom. It may be entirely absent or may be the most outstanding complaint. It may be sudden or gradual in onset, mild or severe in intensity and dull, sharp, burning or cramplike. It usually appears two or three hours after meals (Meyer and Rosenberg,<sup>9</sup> Eusterman, et al<sup>4</sup>). It usually is referred either to the epigastrium or to the right hypochondrium, but occasionally extends over the whole upper part of the abdomen (Brill<sup>3</sup>). It may have no relation to meals or may not be relieved by vomiting.

Constipation is usually present, especially after the onset of vomiting, but may be entirely absent or alternate with diarrhea. The stools may be normal, clay-colored or tarry.

The onset of jaundice depends on the location of the growth. If the tumor arises at or very near the papilla of Vater, jaundice appears early; in fact, it may be the first symptom of the disease. In such instances, it is usually progressive, continuous and often painless, but may entirely disappear or be intermittent, as a result of ulceration and sloughing of the obstructing portions of the growth, of increased intrabiliary pressure forcing the bile through the obstructed papillary opening (Brill<sup>3</sup>) or of subsidence of papillary edema (Meyer and Rosenberg<sup>9</sup>). Otherwise, it is a late symptom due to secondary nodules in the liver, or to compression of the bile duct, either by enlarged adjacent lymph nodes or by extensive growth of a more remote tumor. Occasionally the symptoms of secondary biliary and pancreatic infection arise and complicate the picture.

Fever usually is not present unless there is marked ulceration or secondary biliary infection. It may appear as an accompaniment of terminal toxemia.



## PHYSICAL EXAMINATION

As in any other disease, the general appearance of patients with primary malignant disease of the duodenum varies according to the length of time the disease has been in progress. Thus, early in the disease they may look robust and healthy, the only complaint being a vague discomfort in the upper part of the abdomen, or jaundice may be the first and outstanding feature. On the other hand, when seen later in the course of the disease, as is usually the case, the patients have a cachectic appearance with a pale dry skin, especially after the onset of vomiting.

During a complete examination the attention of the examining physician is directed chiefly to the abdomen. In contrast to that of the lower intestines, in obstruction of the duodenum, the abdomen nearly always is flat, retracted or sunken, owing to lack of fecal and gas retention (Aaron<sup>7</sup> and Brill<sup>3</sup>). However, an existing ascites may cause it to protrude. If there is gastric distention, there is an accompanying fullness in the epigastrium and left hypochondrium, perhaps with a fairly wide area of transmitted aortic pulsation, and gastric peristaltic waves are present. The latter were visible in 5 of 15 cases reported by Eusterman and his collaborators at the Mayo Clinic.<sup>4</sup> Rarely the tumor mass may be seen either fixed or moving with respiration.

Usually the abdominal wall is soft, but occasionally there are epigastric rigidity and tenderness when the pain is severe. The tumor is palpable in from one third (Mayo Clinic<sup>4</sup>) to one half (Brill<sup>3</sup>) of the cases, and is usually small, firm and irregular. The location of the tumor is fairly similar for all portions of the duodenum, being either in the right half of the epigastrium, in the right hypochondrium or near the umbilicus. Growths of the supra-ampullary region of the duodenum are usually quite mobile, while those of the ampullary and infra-ampullary portions are immobile owing to fixation of these portions to the posterior abdominal wall by the peritoneum. Furthermore, careful palpation may reveal gas gurgling through the tumor, especially in the supra-ampullary type. An enlarged liver and gallbladder may be found, particularly if jaundice is present. The liver is usually smooth and firm, but if metastasis has occurred, nodules may be felt. Likewise, peritoneal implantations or greatly enlarged lymph nodes may be palpated. Metastasis to the supraclavicular glands, especially on the left, has been mentioned by Herman and von Glahn<sup>22</sup> and by Meyer and Rosenberg.<sup>9</sup>

By percussion, if the abdomen is protruding, the shifting dullness of ascites can be differentiated from the tympanitic gaseous distention of obstruction of the lower part of the intestines. Occasionally a dilated stomach, and even duodenum, can be outlined.

By auscultation one may detect gurgling of gas through the tumor, a friction rub of local peritonitis, and more commonly a gastroduodenal succussion splash, which was found to be present in 4 of the 15 cases seen at the Mayo Clinic.<sup>1</sup>

#### SPECIAL STUDIES

In the early stages of primary malignant disease of the duodenum studies on the blood throw little light on the disease, but later, after the onset of frequent vomiting or other complications, they are of some value, at least in determining the severity of the disease. The usual finding is a moderate secondary anemia, and if infection is present, there is an accompanying leukocytosis with an increase in polymorphonuclear neutrophils. The van den Bergh test and icterus index should be determined not only when jaundice is present, but also in all cases in which biliary obstruction is suspected. The extreme value of these procedures in combination with the coagulation time is apparent.

Even though the pancreatic duct is completely obstructed, hyperglycemia may never be present or may occur only after considerable time has elapsed. This agrees with the experiments of Kirkbride,<sup>29</sup> who, according to Jefferson,<sup>14</sup> "examined microscopically a portion of the pancreas which had been isolated and had had its ducts ligated fifteen months previously: there was no trace of acinar cells, but the islets of Langerhans persisted and appeared to be actively functioning." The presence and degree of toxemia from duodenal obstruction, which are other important factors, may be determined by the presence of an increase in the carbon dioxide-combining power and in the level of urea with a decrease in the amount of chloride in the blood.

The urine is of high specific gravity if the patient is dehydrated, and usually indicanuria is present. Glycosuria may be present if there is pancreatic damage, and bile is found if there is biliary obstruction.

The stool findings vary according to the degree and site of the obstruction. If bile, pancreatic juice or both are prohibited from entering the lower part of the intestinal tract by obstruction at or below the ampulla of Vater, the stools are characteristic. If bleeding is present, they will be tarry or show occult blood. In addition, they may be normal or may vary from time to time.

Repeated analysis of the gastric contents and vomitus is important. In all the groups free hydrochloric acid usually is diminished, less commonly absent and rarely normal. Of the 12 cases reported by Eusterman,<sup>4</sup> 5 patients had achlorhydria and 7 had diminished free hydrochloric acid. If the obstruction is below the ampulla of Vater, bile and pancreatic juice will be found in the contents of the stomach. Gas-

29. Kirkbride, M.: The Islands of Langerhans After Ligation of the Pancreatic Ducts, *J. Exper. Med.* **15**:101, 1912.

tric motor function depends on the amount of gastric dilatation, being increased during the early stages and decreased later. Careful search may reveal fragments of the tumor.

By roentgenographic examination the exact site of the obstruction can occasionally be determined, as occurred in 2 of 10 cases at the Mayo Clinic.<sup>4</sup> Otherwise, the usual findings are a dilated hypomotile stomach, barium retention and no evidence of any gastric lesion. Occasionally dilatation of the duodenum is prominent. Herman and von Glahn,<sup>27</sup> in their case of annular duodenal carcinoma situated just distal to the pyloric sphincter, emphasized the length of the stalk of barium formed by the lumen of the growth lying between the pylorus and the duodenal cap, which was apparent in the roentgenogram.

#### COURSE AND DURATION

In most cases, primary malignant disease of the duodenum runs a progressive course. The onset usually is insidious, with vague epigastric symptoms and little impairment of the general health, until the growth produces obstruction either of the duodenal lumen, with frequent vomiting, or of the flow of bile, with jaundice. From then on, especially with the interference of nutrition, there is a rapid decrease in the patient's resistance, with a rapidly fatal termination. The terminal phase occasionally is prolonged when there is a spontaneous release of the obstruction by ulceration and sloughing of the growth or when there is surgical intervention. The average duration of the disease generally quoted in the literature is seven months, with the average extremes being three and eighteen months. Intercurrent infection, toxemia of high intestinal obstruction, general inanition and other complications already discussed are the usual causes of a rapidly fatal outcome.

#### DIAGNOSIS

The diagnosis of a primary malignant condition of the duodenum is one of the most difficult problems confronted in medicine, and there are two outstanding reasons for this difficulty. On the one hand, there is a lack of characteristic symptoms and signs with an abundance of features common to several other lesions of the upper part of the abdomen; on the other hand, its rarity, in contrast to the frequency of malignancy in adjacent structures, results in the frequent failure to include it in the differential diagnosis. Consequently, in only a few cases recorded in the literature has the diagnosis even been suspected. Hence most cases were diagnosed either at operation or at autopsy. Some writers have stated that the diagnosis is impossible clinically. However, there are several important steps leading to a possible diagnosis of this condition which should be emphasized. Since primary malignant disease of the duodenum usually manifests itself by obstruc-

tion of the lumen of the intestine, the first step is to decide that the case is one of chronic intestinal obstruction, which can usually be done readily except in the very early cases; then, to locate the obstruction definitely, and finally, to determine the exact cause of the obstruction.

Localization of the lesion is practically impossible in the very early cases of primary malignant disease of the duodenum when there is no clinical or roentgenographic evidence of obstruction. In these cases, the only hope of diagnosis usually lies in exploratory laparotomy. In the later cases, in which the growth has enlarged sufficiently to constrict the lumen of the intestine, there is usually no difficulty in deciding that the case is one of chronic intestinal obstruction and that the obstruction is high in the intestinal tract, in the pylorus, the duodenum or the upper part of the jejunum. The location may be determined by the history of early appearance of gastric symptoms, the lack of gaseous intestinal distention, with the presence of gastric retention and distention, and the absence of fecal vomiting even though the vomiting has persisted for some time. Because of its frequency a lesion of the pyloric end of the stomach must first be ruled out, and this is done chiefly by roentgen examination, by means of which stenosing pyloric gastric lesions may be detected in from 95 to 98 per cent of cases. The next problem is to rule out the jejunum as the site of the disorder. This is done by roentgenographic examination, the absence of feculant material in the vomitus and by the fact that lesions in the jejunum are less likely to cause marked diminution or absence of free hydrochloric acid in the gastric contents. When there is no positive evidence that either the stomach or the jejunum is at fault, it is justifiable to assume, at least temporarily, that the obstruction is in the duodenum. If it is below the ampulla of Vater, bile and pancreatic juice usually are found in the gastric contents on repeated examinations, and the long, dilated, proximal duodenal portion usually is detectable in the roentgenogram. If the lesion is close to the ampulla, evidence of biliary or pancreatic obstruction usually occurs earlier than in obstruction of the other portions of the duodenum, and, if present, together with the characteristic roentgenogram, greatly aids in localizing the lesion. If the obstruction is above the ampulla, roentgen examination must determine its location, or it must be assumed to be in this portion by exclusion of the other two sites.

Having more evidence that the obstruction lies in the duodenum than in the stomach or the jejunum, and perhaps having even limited the obstruction to one of the three duodenal portions, the next problem is to determine the cause of the obstruction. As primary malignant disease of the duodenum has no specific symptoms, signs or special findings, it must be diagnosed chiefly by exclusion of other possibilities. Furthermore, even though the patient's age and the very nature and rapid course of the disease suggest malignancy, there can be no cer-

tainty about this and, therefore, it is necessary to include the possibility of benign lesions in the differential diagnosis. This, of course, greatly increases the number of factors to be kept in mind, but since most of the benign lesions can usually be ruled out quite easily except for a few of the more common ones, no attempt will be made to differentiate them in detail. Except in the very early cases, primary malignant disease of the duodenum has certain features which usually are present and which greatly aid in the differential diagnosis. These are the evidence of chronic high intestinal obstruction; absent or diminished free hydrochloric acid and gastric motility; dilatation of the duodenum, stomach or both; the presence of blood in the feces and gastric contents, and a palpable tumor (in from 30 to 50 per cent of cases) to the right of the midline in the epigastrium or in the region of the umbilicus, which is usually movable in the first portion and fixed in the other two portions of the duodenum.

In diagnosing primary malignant disease of the first portion of the duodenum, pyloric carcinoma is most likely to cause confusion, and the differentiation must be made chiefly by roentgenographic examination. If roentgen examination fails to demonstrate any gastric lesion, but shows duodenal dilatation, there is good reason for excluding the stomach as the site of the disease. Free hydrochloric acid tends to disappear earlier in cases in which there is a gastric lesion than in those in which there is a malignant condition of the duodenum. If a tumor of the stomach is palpable, it usually is less movable and nearer the midline than a tumor in the first portion of the duodenum (Fenwick<sup>17</sup>). In spite of these facts, the differentiation is often impossible. Among the other possibilities, stricture due to a benign peptic ulcer either in the pylorus or in the duodenum sometimes is also difficult to rule out. However, the points against such an ulcer are the usual lack of the characteristic history of ulcer, the more rapid development of emaciation, cachexia and stenosis, a marked decrease or absence of free hydrochloric acid, the presence of a palpable tumor and the failure to demonstrate an ulcer by roentgen examination. Regarding supra-ampullary duodenal obstruction by external pressure, enlargement of the gallbladder is perhaps the most frequent cause, but other causes mentioned by Fenwick<sup>17</sup> are growths of the omentum, kidney, pancreas or liver, enlarged retroperitoneal glands and an aneurysm of the celiac axis or of the hepatic artery. In all of these, in contrast to primary malignant disease of the duodenum, the presence of a comparatively severe obstruction, usually of rapid development, marked cachexia and loss of weight, the presence of blood in the vomitus and stools and a marked decrease or absence of free hydrochloric acid in the gastric secretion are the exception rather than the rule. In addition, roentgen examination may be of value, especially in detecting an enlarged gallbladder.

Duodenal obstruction due to primary malignant disease of the second portion is even more difficult to differentiate from that due to other possible causes, among which a stenosing simple ulcer and pyloric carcinoma have to be considered in the manner already described. Acute pancreatic disease develops much more rapidly, produces less disturbance of digestion and more pain and is less likely to reduce the free hydrochloric acid than is primary malignant disease of the duodenum. Similarly, chronic pancreatitis and pancreatic tumors are less likely to produce obstruction of the duodenal lumen and persistent blood in the feces and vomitus, or greatly to reduce the content of free hydrochloric acid in the gastric secretion. When the lesion is situated at or close to the papilla of Vater and produces jaundice very early in the disease, it is practically impossible to differentiate it from malignant disease of the papilla or the ampulla of Vater, chronic diseases of the pancreas or malignant disease of the gallbladder or the common bile duct, except at operation or autopsy, and even then the differentiation is difficult.

Obstruction of the third or infra-ampullary portion of the duodenum by a primary malignant growth has to be differentiated chiefly from malignant obstruction of the proximal jejunum. For this chief dependence is placed on roentgen examination. Stenosis by a simple ulcer in this portion of the duodenum can usually be ruled out. In addition to the factors opposing a diagnosis of pyloric carcinoma mentioned previously, bile and pancreatic juice usually are not present in the gastric contents in pyloric obstruction unless there is pyloric insufficiency or a gastro-biliary fistula. Furthermore, obstruction of the third duodenal portion by enlarged retroperitoneal glands or superior mesenteric vessels, impaction of a large gallstone or external pressure from a tumor of a contiguous viscus has to be considered.

#### TREATMENT

The value of early surgical intervention has long been recognized in the treatment of primary malignant disease of the duodenum, but only in recent years has the extreme importance of proper preoperative preparation been sufficiently emphasized. Since most cases are complicated either by toxemia of high intestinal obstruction or by jaundice, or occasionally by both, the patients present poor surgical risks, and if they are not properly prepared before operation, their lives may be shortened instead of lengthened by any such procedure.

According to Eusterman,<sup>4</sup> even though toxemia from duodenal obstruction may be suspected clinically, it is chiefly by means of chemical studies of the blood that this condition can be recognized early, its severity measured, the extent of treatment gaged and the effect of treatment determined. Treatment at the Mayo Clinic consists of the administration of from 3,000 to 5,000 cc. of fluid daily by the intravenous, subcutaneous or rectal route; the intravenous injection of from 1,000

to 3,000 cc. of a solution of 1 per cent sodium chloride and 10 per cent dextrose, and gastric lavage once or twice a day. If this treatment is continued daily for a time varying with the individual case, usually for about from four to seven days, marked improvement in the patient's general condition almost invariably results, as shown by daily chemical studies of the blood. In addition, transfusions of blood are especially indicated in these cases.

When jaundice is present, the preoperative treatment is likewise of the utmost importance, owing chiefly to the frequency of death resulting from postoperative hemorrhage. In the 59 cases collected by Cohen and Colp,<sup>30</sup> in which radical operation was performed for malignant disease of the periampullary region of the duodenum, 10, or 40 per cent, of the 25 deaths were due to postoperative hemorrhage. From Barrow, Armstrong and Olds<sup>31</sup> it is learned that in normal blood there is approximately 1 part of bilirubin to 500,000 or 600,000 parts of serum, and that the proportion has to increase to approximately 1 part in 50,000 or 60,000 before clinical jaundice begins to appear. The range of bilirubinemia between the normal dilution and the concentration necessary to cause the first appearance of clinical jaundice is known as "latent jaundice." In terms of icterus index, the normal range is between 4 and 6, latent jaundice is between 6 and 15, and clinical jaundice usually appears above 15. When jaundice is evident, the necessary precautions are usually taken, but when the jaundice is latent, it may give rise to unsuspected operative hemorrhage, unless it has been recognized and properly treated before operation. Therefore, the importance of performing the van den Bergh test, icterus index and studies on the coagulation of blood in all of these cases cannot be overestimated. For the preoperative preparation of jaundiced patients there is the method of Walters,<sup>32</sup> recommended by Cohen and Colp,<sup>30</sup> consisting of the daily administration of 5 cc. of 10 per cent calcium chloride solution intravenously for three days; 100 grains (6.5 Gm.) of calcium lactate by mouth daily for four days; 4,000 cc. of water by mouth daily; proctoclysis by means of a Murphy drip one hour on and one hour off, from 3 to 15 per cent solution of dextrose being used; a high carbohydrate diet or a 10 per cent solution of dextrose intravenously, which, according to Mann and Magath,<sup>33</sup> is almost specific for hepatic insufficiency,

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30. Cohen, I., and Colp, R.: Cancer of Periampullary Region, Surg., Gynec. & Obst. **45**:332, 1927.

31. Barrow, J. V.; Armstrong, E. L., and Olds, W. H.: A Clinical, Pathological and Operative Study of the Icterus Index, Am. J. M. Sc. **169**:583, 1925.

32. Walters, W.: Pre-Operative Preparation of Patients with Obstructive Jaundice, Surg., Gynec. & Obst. **33**:651, 1921.

33. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver, Am. J. Physiol. **55**:285, 1921.

and also a transfusion of blood, given from twenty-four to forty-eight hours before operation, if the patient does not respond to the other measures. By this method Walters<sup>32</sup> was able to reduce the coagulation time of the blood from fourteen minutes to two minutes in some cases. Judd<sup>34</sup> sanctioned this treatment, but expressed the belief that it is better to continue it for one or two weeks instead of for only three or four days, as recommended by Walters.<sup>32</sup>

The type of operative procedure in primary malignant disease of the duodenum depends on the condition of the patient, the size and location of the growth and the presence or absence of complications, such as jaundice or metastases. In the uncomplicated cases, if the growth is very small, excision of the growth and a small amount of surrounding healthy tissue may be all that is necessary, but if the growth is larger or encircles the duodenum, a radical resection of the affected portion of the intestine should be done with or without gastro-enterostomy or transplantation of the biliary and pancreatic ducts into the duodenal wall. In 1 case, according to Outerbridge,<sup>26</sup> a small growth was simply curretted away and the site cauterized. When jaundice is present and the growth is small and localized to the immediate region of the papilla, Cohen and Colp<sup>30</sup> recommend radical excision of the growth and reimplantation of the biliary and pancreatic ducts into the duodenum, but if the tumor is inoperable, the biliary obstruction should be relieved by cholecystogastrostomy, cholecystoduodenostomy, cholecystenterostomy or cholecystostomy. If the gallbladder has been removed previously or if the case is unadaptable for anastomosis, a choledochoduodenostomy or a choledoch-enterostomy may be performed. On the other hand, if the patient's condition does not justify radical excision, the two stage method used by Mayo<sup>35</sup> and Kausch<sup>36</sup> may be followed, in which a palliative operation, such as cholecystenterostomy or gastro-enterostomy, is performed to relieve distressing symptoms, followed later, in their cases in two or three months, respectively, by the radical operation. When metastases are present without evidence of biliary obstruction, a palliative gastro-enterostomy alone is a justifiable procedure.

#### OPERATIVE RESULTS

Since the average length of life of patients with primary malignant disease of the duodenum, especially of the ampullary region, is generally quoted as being from six to eight months, in spite of palliative measures.

34. Judd, E. S.: *Surgical Procedures in Jaundiced Patients*, Collected Papers of the Mayo Clinic, Philadelphia, W. B. Saunders Company, 1925, vol. 17, p. 125; *J. A. M. A.* **85**:88 (July 11) 1925.

35. Mayo, W. J.: *A Case of Carcinoma of the Duodenal End of the Common Duct with Successful Excision*, *St. Paul M. J.* **3**:374, 1901.

36. Kausch, W.: *Die Resektion des mittleren Duodenum*, *Zentralbl. f. Chir.* **36**:1350, 1909.



the question arises as to what are the results when radical procedures are undertaken in these cases. In the 59 cases collected by Cohen and Colp<sup>30</sup> in 1927, in which radical operation of the ampullary region had been performed, the operative mortality was 44 per cent. Table 7 shows the length of life of those who survived the operation and lived for more than six months. In a similar series of 81 cases collected by Muller and Rademaker<sup>37</sup> in 1931, 16 patients, or 19.7 per cent, lived more than one year, 7 patients, or 8.6 per cent, lived four years or more, 2 patients lived five years, 2 six years, 1 nine years and 1 twenty-two years. In all of these, a transduodenal excision with reimplantation of the common duct was performed. In this same series, there was 1 case in which the patient lived for five years after merely a palliative cholecystoduodenostomy was performed. If symptoms develop after a radical operation has been performed, they should be relieved by palliative

TABLE 7.—*Results of Radical Operations for Carcinoma of the Ampullary Region of the Duodenum (Cohen and Colp<sup>30</sup>)*

Years Alive	Number of Cases	Per Cent
0 to ½.....	27	45.8
½ to 1.....	14	23.7
1 to 2.....	6	10.1
2 to 3.....	3	5.1
3 to 4.....	3	5.1
4 to 5.....	1	1.6
5 to 9.....	0	0.0
9 to 10.....	1	1.6
Recovery but no time stated.....	4	6.8

measures, which often greatly prolong the life of the patient, as illustrated by a case reported by Muller and Rademaker<sup>37</sup> in which there was a five year cure. Strauss, Block, Friedman and Hamburger<sup>38</sup> reported a case in which there was a lymphosarcoma located distal to the ampulla of Vater; the patient survived two years after pyloric closure and gastro-enterostomy followed by a course of high voltage roentgen therapy. Schofield,<sup>12</sup> in 1930, reported a case in which cholecystoduodenostomy and posterior gastro-enterostomy were performed, followed by implantation of radon seeds in the adenocarcinomatous growth located on the posteromedial wall of the duodenum in the ampullary region. Autopsy twenty-nine days later showed a fistula in the anterior surface of the duodenum, but the wall at the site of the

37. Muller, G. P., and Rademaker, L.: End-Results in Radical Operations for Carcinoma of Periapillary Region of Duodenum, *Ann. Surg.* **93**:755, 1931.

38. Strauss, A. A.; Block, C.; Friedman, J. C., and Hamburger, W. W.: Sarcoma of Duodenum and Stomach, *S. Clin. North America* **5**:977, 1925.

malignant growth was intact, the growth was difficult to identify grossly, and there was complete absence of cancer cells in many microscopic sections.

Following are the reports of 2 cases of duodenal carcinoma observed at the Cleveland Clinic.

#### REPORT OF CASES

**CASE 1.—History.**—A married woman, aged 53, was admitted to the Cleveland Clinic Hospital on Dec. 20, 1931, with persistent and progressive symptoms of ten months' duration, which included frequent, dull, epigastric pain, gas formation, loss of 39 pounds (17.7 Kg.), a marked decrease in strength and frequent nausea and vomiting; the pain always was limited to the epigastrium, never radiated,



Fig. 1 (case 1).—Roentgenogram taken following a barium meal, showing dilatation of the stomach and of the duodenal bulb.

appeared at any time of the day or night, lasted from a few minutes to several hours, usually was relieved by vomiting and always was followed by soreness in the region of the gallbladder. There had never been hematemesis, jaundice, fever or chills. There had been varying degrees of constipation, but never any diarrhea. The stools frequently were light yellow, but never tarry. There was nothing in the past history or in the family history which had any bearing on the case.

**Examination.**—The patient was a small woman, only 4 feet, 9 inches (144.8 cm.) in height, weighing 99 pounds (44.9 Kg.), who, in spite of having lost 39 pounds, did not look emaciated. The skin appeared to be of normal color and texture. The temperature was 98.6 F.; the pulse rate was 110, and the blood pressure was 150 systolic and 70 diastolic. Oral examination showed receding gums, marked pyorrhea and small, chronically infected tonsils. The heart sounds were normal except for a soft systolic aortic murmur. There was moderate sclerosis of the peripheral vessels. The abdomen was flat and soft, and there was no palpable

mass. The liver and gallbladder were not enlarged, but there was slight tenderness in the region of the gallbladder. Rectal examination was negative except for a few small external hemorrhoids.

The blood count was normal, with 4,840,000 erythrocytes, 9,700 white cells and a hemoglobin content of 84 per cent. Repeated urinalyses showed nothing abnormal. The Wassermann and Kahn reactions were negative. Gastric analysis could not be done because of nausea and vomiting. The blood sugar was 97 mg. per hundred cubic centimeters, and the blood urea, 51 mg. Roentgen examination failed to reveal the gallbladder because the dye had not been properly absorbed. The barium meal showed a hugely dilated stomach and duodenal bulb (fig. 1) without evidence of any organic defect, but just beyond the duodenal bulb there was an obstructive lesion that was constant in all positions. There also was evidence of residue in the stomach and duodenal bulb, after six hours, but none at



Fig. 2 (case 1).—Section of the adenocarcinoma; reduced from  $\times 150$ .

twenty-four hours, showing that the obstruction was not complete. The colon seemed completely normal.

*Operation and Course.*—An operation, performed on Dec. 24, 1931, by Dr. R. S. Dinsmore, revealed a large, dilated stomach and duodenal bulb caused by a hard, nodular, ringlike growth 1 inch (2.5 cm.) in width completely encircling the second portion of the duodenum about 3 inches (7.6 cm.) beyond the pylorus. There was no evidence of metastasis, and the gallbladder and ducts were normal. Biopsy showed the growth to be adenocarcinoma (fig. 2). A palliative posterior gastro-enterostomy was performed.

The patient made an uneventful operative recovery and was discharged on the sixteenth day after operation. Her symptoms had been completely relieved. She was seen about three weeks later, complaining of diarrhea and hemorrhoids, which were treated. Jaundice first appeared on Feb. 9, 1932, just a month following her discharge from the hospital, and because it was progressive, continuous and accom-

panied by intense itching, she was admitted to the Cleveland Lutheran Hospital on April 4. Examination at that time showed that she was quite jaundiced and emaciated. Her weight was only 79 pounds (35.8 Kg.). The liver and gallbladder were moderately enlarged and tender. Examination of the blood showed that anemia had developed; the erythrocytes numbered 3,700,000; the white blood cells, 5,000, and the hemoglobin had dropped to 68 per cent; the icterus index was 101. A cholecystostomy was performed on April 6 by Dr. W. E. Lower, followed by an uneventful operative recovery and a rapid subsidence of the itching and jaundice. The patient was discharged in good condition on April 18. Four months later, in August, she was much improved, had gained 30 pounds (13.6 Kg.), and was doing her own housework. The bile was draining freely through the cholecystostomy wound, and the stools were white. The patient was free from any distressing symptoms.<sup>39</sup>

*CASE 2.—History.*—A married woman, aged 50, was admitted to the Lakeside Hospital on July 3, 1918. She had had a cholecystectomy in March, 1917, which was performed at another hospital and of which no record was obtainable, following which there were a gradual loss of 68 pounds (30.8 Kg.), a marked decrease in strength, marked constipation, requiring daily cathartics and enemas, and attacks of vomiting, lasting from two to three days and recurring from every three to six weeks, which were usually accompanied by either soreness or moderate cramplike pain in the epigastrium. The vomitus was usually of a yellowish-green color and on two occasions had contained food ingested forty-eight hours previously. There had been no jaundice at any time. The past history and family history were irrelevant except that the patient had typhoid fever in 1889.

*Examination.*—The patient had a flat abdomen with marked tenderness and slight rigidity in the epigastrium. The liver and spleen were not enlarged. No circumscribed mass was palpable.

Examination of the blood showed 4,480,000 erythrocytes, 8,200 leukocytes and 70 per cent hemoglobin; the Wassermann reaction was negative. The urine was acid and contained albumin, a few white blood cells, epithelial cells, casts, mucous shreds and uric acid crystals. Gastric analysis showed an absence of blood and mucus and the presence of bile and a few undigested particles of food. Gastric analysis ten days later again showed an absence of free hydrochloric acid and a total acidity of 20 per cent, but this time every specimen contained free blood.

*Operation and Course.*—On July 29, 1918, operation by Dr. W. E. Lower revealed a hard, carcinomatous mass, 1 inch (2.5 cm.) in length, obstructing the third portion of the duodenum 7 inches (17.8 cm.) distal to the pylorus. There was no evidence of metastasis. A radical resection of this portion of the duodenum with a lateral anastomosis and appendectomy were performed.

The patient made an uneventful operative recovery and was discharged on August 21 in good condition. She lived until Sept. 20, 1924. The exact cause of death was not known. No autopsy was obtained.

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<sup>39</sup> The patient's condition was satisfactory until late in January, 1933, when drainage from the cholecystostomy opening ceased, jaundice and itching recurred, and a large mass was palpable in the right upper part of the abdomen. She failed rapidly, and died about three weeks later. Autopsy was refused, but the clinical signs and symptoms indicated that there had been extension of the growth and obstruction of the common bile duct.

## CONCLUSIONS

1. Primary carcinoma of the duodenum is found in 0.033 per cent of autopsies, making the ratio 1:2,780. Although it is a rare disease, a sufficient number of cases have been reported to arouse clinical interest.
2. It is almost as frequent as carcinoma of the jejunum and ileum combined.
3. It occurs three times as frequently in men as in women.
4. The sixth decade of life is the average and most frequent period in which this disease occurs.
5. Of the three duodenal portions, the second or ampullary is by far the most frequently involved.
6. Cylindric cell adenocarcinoma, with its tendency to encircle and obstruct the duodenum, is the type most frequently found.
7. There is little evidence that malignant disease of the duodenum ever arises from a simple duodenal ulcer.
8. Metastases, even to the contiguous lymph nodes, are not common, and generally occur very late in the disease.
9. Since primary malignant disease of the duodenum has no characteristic symptoms, signs or special findings, the diagnosis is most difficult.
10. The course of the disease is usually progressive and rapid.
11. Radical excision should be performed in the uncomplicated cases; otherwise, palliative measures are justifiable.
12. More thorough preoperative preparation is one method of reducing the existing high operative mortality in these cases.
13. So few cases of primary sarcoma of the duodenum have been reported that it is impracticable to draw any conclusions regarding them. However, sarcoma is generally thought to occur less frequently and at an earlier age than carcinoma and to be more responsive to high voltage roentgen therapy.

# NASOPHARYNGEAL CARCINOMA

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A review of the reports of nasopharyngeal carcinomas is made difficult by the various titles used to describe them. To some extent this confusion exists because of variations in the structural arrangement and meager differentiation of the tumor cells, but especially because these tumor tissues have been found metastatic in cervical lymph nodes and the primary focus was not considered, or was overlooked during the life of the patient, or in the body when the postmortem examination was made. Consequently, the metastases in the lymph nodes were regarded as primary growths, and the alinement of the observations with such an interpretation brought confusion. Among the descriptive titles used are carcinoma, epithelioma, transitional cell carcinoma, lympho-epithelioma and endothelioma as well as others when the reports are without an adequate gross or histologic description. The review of nasopharyngeal carcinoma by Norcross<sup>1</sup> in 1913 mentioned about fifty-five growths, and at the end of 1931 there were less than eighty more. Because of marked radiosensitivity and histologic structure, some authors have described certain of these tumors as transitional cell epidermoid carcinoma in contradistinction to the squamous cell variety. Thus, Crowe and Baylor,<sup>2</sup> Quick and Cutler,<sup>3</sup> and Hughes<sup>4</sup> together have reported nineteen such tumors. They contend that this tumor has a specific histologic structure. The growths have small closely arranged cells with scanty cytoplasm and hyperchromatic nuclei, and only a small amount of intercellular substance. The primary focus of these carci-

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From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Norman Bridge Pathological Laboratory of Rush Medical College of the University of Chicago.

1. Norcross, E. P.: Intramural Malignant Tumor of the Lateral Wall of the Nasopharynx, *Ann. Otol., Rhin. & Laryng.* **25**:967, 1916.

2. Crowe, S., and Baylor, J.: Benign and Malignant Growths of the Nasopharynx and Their Treatment with Radium, *Arch. Surg.* **6**:429 (March) 1923.

3. Quick, D., and Cutler, M.: Transitional Cell Epidermoid Carcinoma, *Surg., Gynec. & Obst.* **45**:320, 1927.

4. Hughes, T. E.: Transitional Cell Epithelioma of the Nasopharynx, *South. M. J.* **22**:826, 1929.

nomas is usually small, and the nasopharynx is not the only site of origin. In fact, they occur more frequently at the base of the tongue, in the tonsil and larynx, but the metastases into the neck from such sites of origin are unilateral. Contrasting with the squamous cell carcinoma, the transitional cell tumors rapidly produce large metastases to the cervical lymph nodes and viscera, and they are markedly radiosensitive. The tissues never have mature squamous epithelial characteristics such as hornification, spines or pearl formation. According to Quick and Cutler, these carcinomas may arise from the transitional epithelium lining portions of the nasopharynx, ducts of mucous glands, or, as they state, by a reversion from metaplastic or anaplastic squamous epithelium. Finally, these growths are said to develop from misplaced embryonal tissues.

Ewing<sup>5</sup> concluded that the transitional cell carcinoma cannot be separated sharply from the so-called lympho-epithelioma. The latter tumor, he maintained, arises from a modified epithelium overlying lymphoid structures at the base of the tongue, in the nasopharynx and in the tonsils. Schmincke,<sup>6</sup> Ferreri,<sup>7</sup> and others, however, stated that a lympho-epithelioma is a specific tumor and should not be confused with a transitional cell carcinoma. Beck and Guttman,<sup>8</sup> and Cutler<sup>9</sup> have published concise reviews of the literature relating to these two varieties of tumors. Clinically they cannot be differentiated from one another since both are extremely radiosensitive and both, as a rule, promptly produce extensive metastases. Schmincke stated that a lympho-epithelioma has a branchiogenic origin as has the normal lymphoid tissue, and that this tumor is distinctive in consisting of a syncytial reticulum infiltrated with lymphocytes both in its primary growth and in its metastases. Dietrich<sup>10</sup> and Babès<sup>11</sup> stated that the

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5. Ewing, J.: Radiosensitive Epidermoid Carcinomas, *Am. J. Roentgenol.* **21**:313, 1929; Lymphoepithelioma of Nasopharynx, *Am. J. Path.* **5**:99, 1929.

6. Schmincke, A.: Ueber lymphoepitheliale Geschwülste, *Beitr. z. path. Anat. u. z. allg. Path.* **68**:161, 1921.

7. Ferreri, G.: Zur Diagnose und Therapie der Lymphoepithelioma des Nasenrachens, *Acta otolaryng.* **9**:441, 1926.

8. Beck, J., and Guttman, R.: The Relation of the Histopathology of Nasopharyngeal Neoplasms to their Radiosensitivity, *Ann. Otol., Rhin. & Laryng.* **41**:349, 1932.

9. Cutler, M.: Radiosensitive Intra-Oral Tumors, *Arch. Surg.* **18**:2303 (April) 1929.

10. Dietrich, A.: Geschwülste des Rachens, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, p. 14.

11. Babès, A.: Les tumeurs lympho-épithéliales, *Ann. d'anat. path.* **6**:1105, 1929.

lymphocytes present even in the metastases are secondary infiltrations. Singer<sup>12</sup> reported one tumor that resembled equally a small undifferentiated sarcoma and a lympho-epithelioma. He considered the latter tumor a special form of sarcoma and consequently of mesenchymal origin.

In contrast to these two varieties of radiosensitive tumors briefly discussed, mention should be made of a group of tumors that clinically is characterized by a marked resistance to radium and which rarely produces generalized metastases. These are the squamous cell carcinomas. A search has failed to demonstrate any report of a primary nasopharyngeal carcinoma having fully differentiated squamous epithelial cells. Several nasopharyngeal carcinomas without visceral metastases have also been described as epithelioma, papillary and glandular carcinoma, and as carcinoma simplex.

Oppikofer,<sup>13</sup> Gatewood,<sup>14</sup> Citelli<sup>15</sup> and Singer together have reported fourteen tumors with complete histologic descriptions. Of these tumors, five had a tendency to form stratified pavement epithelium, four glandular structures, one a papillary structure, and five were simply designated as carcinoma simplex. In addition, Hansel<sup>16</sup> studied ten carcinomas and prepared a summary of their histologic characteristics. These growths were highly malignant, and their cells lacked differentiation. The tissue structure of Hansel's tumors was remarkably like that described by other authors as transitional cell carcinoma. The exact origin of these tumors, and whether the so-called transitional cell carcinoma is only its more immature and malignant form, is uncertain. Dietrich has proposed that a remnant of a hypophyseal stalk is the source of a few of these growths, that is, of those located in the midline. Rosenbusch<sup>17</sup> stated that embryonal rests of the hypophyseal stalk consisting of nests of squamous epithelium have been found normally in all adults. Dietrich reported that these tumors are more often a variety of immature squamous epithelium, and conceivably such indif-

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12. Singer, L.: Zur pathologischen Anatomie der malignen Geschwülste im Nasenrachenraum, *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **17**:368, 1927.

13. Oppikofer, E.: Ueber die primären malignen Geschwülste des Nasenrachenraumes, *Arch. f. Laryng. u. Rhin.* **27**:526, 1913

14. Gatewood, W. E.: Carcinomas of the Nasopharynx, *J. A. M. A.* **66**:499 (Feb. 12) 1916.

15. Citelli, C.: Ueber 10 Fälle von primären malignen Tumoren des Nasenrachens, *Ztschr. f. Laryng., Rhin., Otol.* **4**:331, 1911.

16. Hansel, J. K.: Malignant Tumors of the Nasopharynx, *Arch. Otolaryng.* **9**:12 (Jan.) 1929.

17. Rosenbusch, H.: Ueber das Karzinom des Nasenrachenraumes im frühen Kindesalter, *Frankfurt. Ztschr. f. Path.* **31**:507, 1925.



ferent tumors as the carcinoma simplex arise from an embryonal type of undifferentiated epithelial cells. These immature tumors in turn may differentiate into the other more mature varieties of carcinomas. Singer believed that the tumors arise from the stratified squamous and the pseudostratified columnar epithelium of the nasopharynx, and that the more differentiated, and hence the less malignant they are, the more they resemble these linings. The latter view seems the most plausible. The scanty differentiation of the epithelium in the carcinomas described as transitional cell carcinomas or lympho-epithelioma probably is only such as occurs in indifferent epithelium arising from squamous cell surfaces. These immature squamous cell carcinomas probably would be more radiosensitive, more malignant, and cause earlier and more extensive metastases than the more mature variety.

The rarity of nasopharyngeal carcinomas can be appreciated from the statistics of the Charité Hospital in Berlin where they constituted only 1.67 per cent of all carcinomas of the body. Singer in ten years found nasopharyngeal carcinomas in only two of 7,051 bodies.

Grossly, there is nothing characteristic about the primary tumor whereby it can be classified into any special variety of carcinoma. It is usually small, often not more than 0.5 cm. in diameter. The surface may ulcerate and the growth is slow. New<sup>18</sup> stated that the average duration of clinical symptoms is fourteen months, but this probably varies. Both sexes are affected equally, and the tumor may occur at any age. According to Gatewood, 60 per cent of the patients are between the ages of 40 and 60 years. The youngest patient was 1 year, 3 months of age.

The clinical symptoms vary markedly, and the disease often remains unrecognized for some time. If the tumor extends laterally, as is often the case, the eustachian tube becomes involved and the subsequent symptoms are referable to the ear. One of the first and most important symptoms is an insidious enlargement of the cervical lymph nodes because of tumor metastases. The patient usually notes the slow growth of a painless nodule in the parotid or carotid region on one side of the neck, and frequently several weeks or months later a similar growth on the opposite side. Many of these enlarged glands have been erroneously diagnosed as endotheliomas, even when tissues were excised for examination, because a growth of the nasopharynx was not suspected or sufficient care was not exercised in examining the nasopharynx to disclose the primary growth. When the tumor extends anteriorly, symptoms of nasal obstruction or bleeding occur. The extensions may be into the sphenoid, ethmoid and frontal sinuses, and occasionally into

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18. New, G. B.: Syndrome of Malignant Tumors of the Nasopharynx, J. A. M. A. 79:10 (July 1) 1922.

the anterior cerebral fossa. Then, any or all of the second, third, fourth, second and third branches of the fifth and the sixth cranial nerves are involved, causing an enigma of symptoms unless the primary tumor is found. When the tumor extends down into the tissues of the pharynx and particularly when the tumor tissues compress the ninth, tenth, eleventh and the twelfth cranial nerves at their exit from the jugular foramen, Jackson's syndrome, complete or partial, is present. Extension posteriorly is rare. If this occurs, the bones at the base of the skull are eroded, the brain is compressed and symptoms of a basal brain or pituitary tumor develop. The neurologic symptoms produced by these tumors were summarized concisely by Woltman.<sup>19</sup> New, in reviewing the symptoms of seventy-nine patients with malignant tumors of the nasopharynx, mentioned that of these only thirty-eight had nasopharyngeal symptoms. He, therefore, emphasized the importance of nasopharyngeal examinations in patients having unexplained symptoms referable to the pituitary body or to the gasserian ganglions, symptoms of a brain tumor or glandular enlargements of the neck, and in those with a metastatic malignant tumor of the body where the primary focus is concealed. Even then, the primary nasopharyngeal growth may be too small or too deeply seated to be detected without special effort. Of interest in this connection is the circumstance that the first examination of the nasopharynx in each of the three patients of our report failed to demonstrate the primary carcinoma, notwithstanding that the examining physician knew of the bilateral enlargement of the cervical lymph nodes and that the pathologists considered the carcinoma tissues found in excised nodes secondary to a primary growth of the nasopharynx.

#### REPORT OF CASES

CASE 1.—G. H., a white man, aged 36, entered St. Luke's Hospital on Nov. 3, 1931, with bilateral enlargement of the cervical lymph nodes for more than two years; persistent pain in the occipital region, cough and hemoptysis for three months, and a loss in weight of 17 pounds (7.7 Kg.) in five months. The swelling in the left cervical region was noticed shortly before that in the right. On arising in the morning, he expectorated a small amount of blood-tinged, yellow mucus. His tonsils had been removed many years before. At the age of 12 years he injured his head while diving. Shortly thereafter he noticed a swelling in the left cervical region which persisted for one and a half years. At the angle of the jaw and extending upward on both sides of the neck were firm and fixed masses, about the size of a hen's egg. No other lymph node enlargements were noted. There were no unusual elements in the urine. The blood pressure was 140 systolic and 80 diastolic. The blood had 4,300,000 erythrocytes and 17,750

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19. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, *Arch. Neurol. & Psychiat.* 8:412 (Oct.) 1922; Involvement of the Nervous System in Malignant Disease of the Nasopharynx, *M. Clin. North America* 7:309, 1923.

leukocytes per cubic millimeter, of which 85 per cent were polymorphonuclear leukocytes, 10 per cent monocytes, 10 per cent lymphocytes and 2 per cent band cells. The hemoglobin was 80 per cent (Sahli). The temperature was 97.2 F., the pulse rate was 90, and the respirations were within usual limits. The roentgenologic examinations of the head, neck and thorax disclosed calcified tissues in the masses of the right side of the neck, a thickening of the lateral processes of the first and second cervical vertebrae, changes in the occipital bone posterior to the foramen magnum with new bone growth suggesting an inflammatory process rather than a malignant growth, and changes of the upper part of the right lung, but not those of recent pulmonary tuberculosis. The sinuses of the cranium were unchanged. A clinical diagnosis of bilateral tuberculosis of the cervical lymph glands was made. On Nov. 6, 1931, the enlarged right cervical lymph glands were removed, and an abscess in this region was drained. The patient made an uneventful recovery from the operation and was discharged within a few days. Dr. E. R. LeCount reported carcinoma metastases in these cervical lymph nodes, and the primary growth, he concluded, was probably in the nasopharynx. The primary nasopharyngeal carcinoma was demonstrated by Dr. M. Bryed Wilson. Death occurred on June 1, 1932, after a lingering illness.

The body was examined at St. Luke's Hospital at 9:00 a. m., on June 2, 1932, by Dr. Edwin F. Hirsch. The essentials of the anatomic diagnosis were: primary carcinoma of the posterior wall of the nasopharynx; carcinoma infiltration and erosion of the clivus and regional bones of the cranium; carcinoma compression of the pons and cerebellum; metastatic carcinoma of the right and left upper deep cervical lymph nodes; carcinoma thrombosis of the left internal jugular vein and of some of its superior branches; marked necrosis and liquefaction (pseudo-abscess) of the metastatic tumor tissues of the neck; confluent bronchopneumonia of the right lung; acute exudative otitis media on the right side; hyperemia and edema of the right lung; cloudy swelling of the liver, kidneys, and myocardium, and marked emaciation.

A mass about the size of a small hen's egg beneath a healed surgically incised wound in the right mastoid and carotid regions involved the upper part of the sternomastoid muscle and extended to the base of the cranium. The upper portion of this mass contained an abscess from 4 to 5 cm. in diameter with about 20 cc. of a thin, gray, purulent fluid. The wall was gray-white, soft and friable tumor tissue. The right lower deep cervical lymph nodes behind the carotid sheath were 1 cm. in diameter and consisted grossly of unchanged lymphoid tissue. The corresponding left lymph nodes were 2 cm. in diameter and consisted of a firm, gray-white tumor tissue that extended into the region of the ear tissues behind the angle of the jaw. The tumor tissue also had penetrated the adjacent wall of the internal jugular vein and occluded 4 cm. of the lumen. The lumen of the upper portion of the left external jugular vein was filled with a firmly adherent, gray-white, finely trabeculated thrombus that extended 7 cm.

A block of tissues was cut out of the base of the cranium (fig. 1), and the important portions and structures included were the clivus, sphenoid and ethmoid bones, nasal and postnasal spaces, hard and soft palate and the first and second cervical vertebrae. The postnasal space was narrowed by a finely nodular, firm and gray-white growth, 10 by 10 by 4 mm., protruding from the posterior wall of the nasopharynx. The upper edge was about 1 cm. from the vault of the nasopharynx. It occupied the midline, but extended more to the right

than the left side and was covered with a glistening mucosa. The mucosa lining the remaining portions of the nasopharynx was smooth and glistening. Posteriorly, the growth had infiltrated extensively the body of the sphenoid bone, and it reached to the floor of the sella turcica. The basilar portion of the occipital bone and the bodies of the first and second cervical vertebrae were similarly ingrown by tumor tissue. The carcinoma had penetrated the dura of the clivus and had grown into an elevated mass of gray, granular tissue, 2 by 2.2 by 0.4 cm., to the right of the midline. This extended to within 3 mm. of the right internal auditory meatus and extended down 1.5 cm. on the lateral side of the spinal cord. Medially and to the left of this mass, the clivus was elevated 1 cm. and was covered with a smooth dura. There were no gross changes of the lining or deep tissues of the floor and roof of the nasal passages, hard and soft palate, nasal

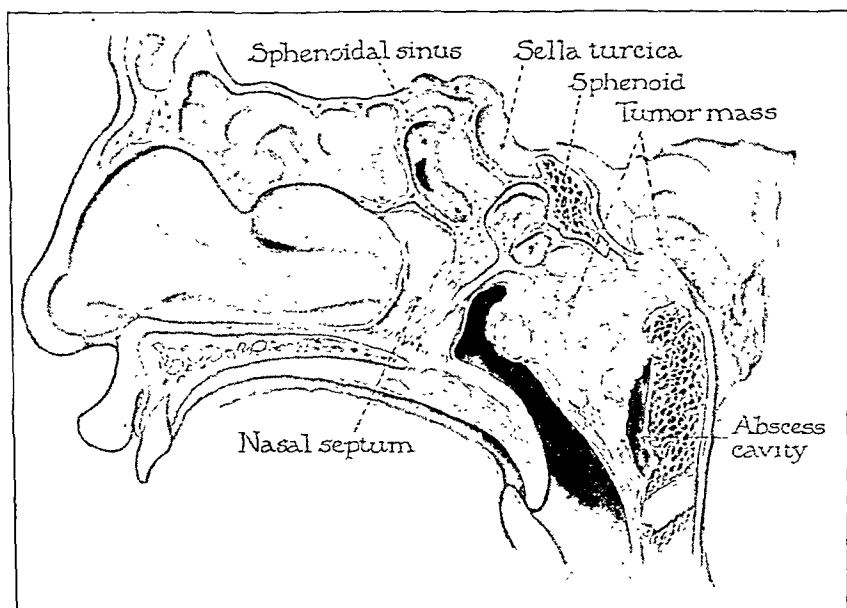


Fig. 1 (case 1).—Sketch of a sagittal view of the nasopharynx to illustrate the location of the primary carcinoma and the erosion of the clivus.

septum, middle and superior turbinate bodies, uvula, or of the ethmoid, frontal, maxillary or sphenoid sinuses.

*Histologic Report.*—Right Cervical Lymph Gland Removed Surgically: Four pieces of tough, red, fibrous and lymphoid tissues ranged from 1.8 by 1.6 by 1.2 cm. to 4 by 3 by 1.2 cm. One piece was a gritty calcified mass 2.5 by 2 by 1.2 cm. Another piece also contained a firm fibrocaseous region 4 mm. in diameter. These tissues histologically had narrow and wide sinuous bands of dense hyalinized fibrous tissue ingrown about 40 per cent by branched cords and masses of epithelial cells laid down in mosaics (fig. 2). The cells varied considerably in size. Most of them were small, but many were large and undifferentiated. They had large round and oval vesicular nuclei surrounded by a small amount of basophilic cytoplasm. Many large cells were in mitosis. These tumor cells had no tendency to assume a definite arrangement. There was no hornification of the

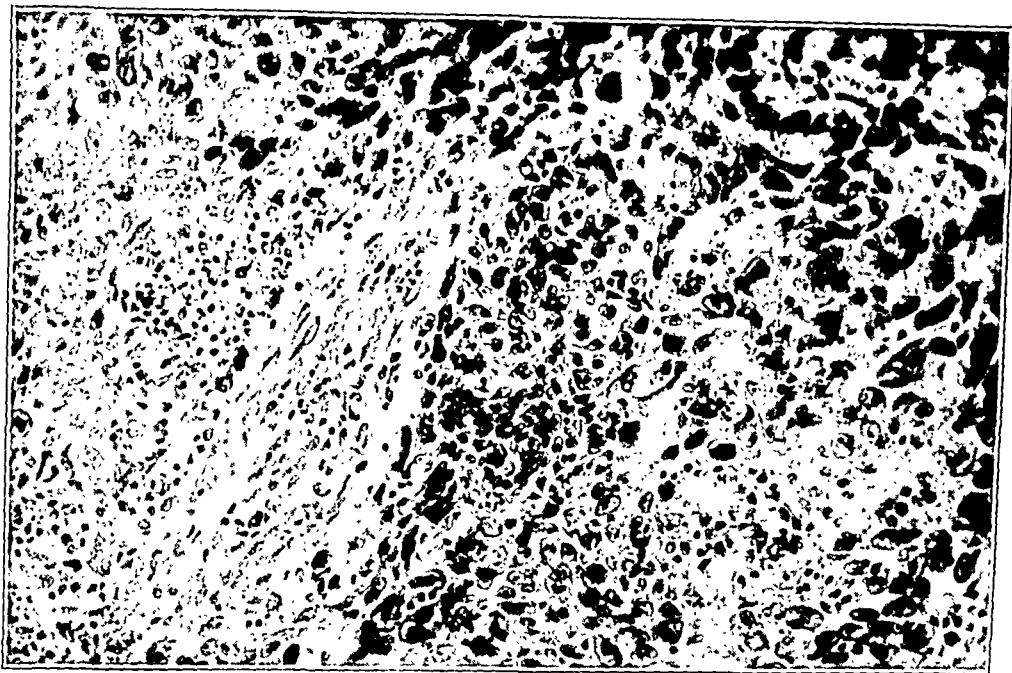


Fig. 2.—Photomicrograph illustrating the carcinoma metastases in the right cervical lymph nodes. These tissues were removed surgically with the diagnosis of tuberculosis, and the histologic examinations gave the first intimation of a primary carcinoma of the nasopharynx. Reduced from a magnification of  $\times 252$ .

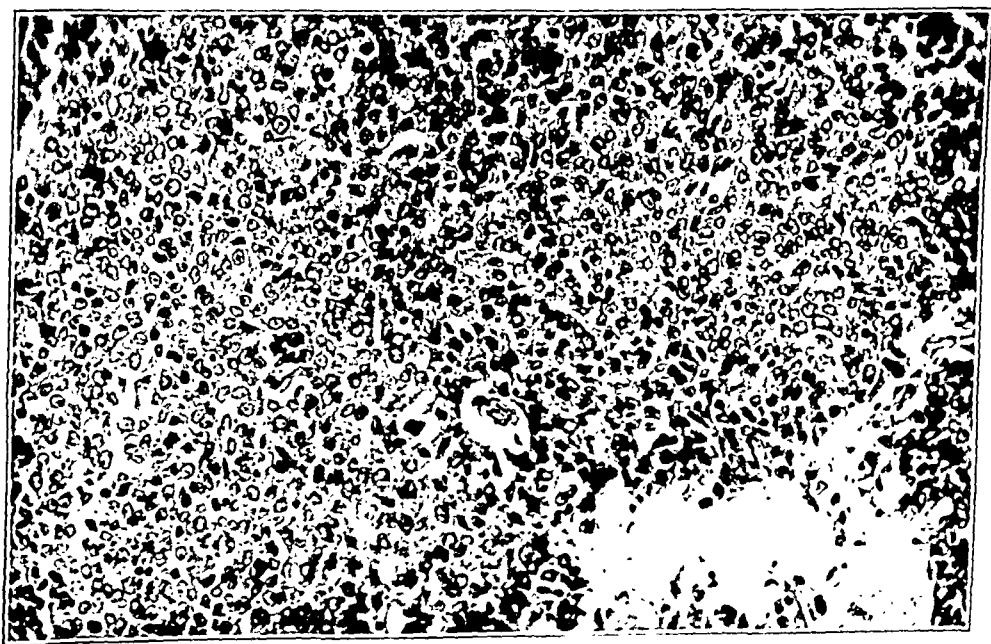


Fig. 3.—Photomicrograph of the carcinoma tissues metastatic in the left cervical lymph nodes. These tissues were obtained during the postmortem examination. Reduced from a magnification of  $\times 252$ .

cells or so-called "epithelial pearls." Focally, in the fibrous tissues were chronic inflammatory changes. Only small masses of lymphoid tissue remained.

During the postmortem examination, tissues were taken from the tumor mass in the left side of the neck for microscopic examination. These tissues had essentially the same structure as those in the right cervical gland, except that there were fewer large cells and only occasional cells in mitosis (fig. 3). These carcinoma cells also had no orderly arrangement except in a few places where they tended to be in stratified layers of varying width. At the base, the cells and their nuclei were elongated like those of columnar epithelium; they were more polyhedral near the surface, not unlike the structure of stratified squamous epithelium. Focally, there were regions of chronic inflammation and necrosis of the fibrous tissue. The histologic structure of the primary growth was essentially the same. The left cervical lymph nodes and tissues from the wall of the abscess of the cervical spine and from the thrombosed left external jugular vein were invaded by similar carcinoma tissues. The cells, however, were arranged even more orderly and had a closer resemblance to stratified squamous epithelium. There was no necrosis in these metastases.

CASE 2.—A white man, aged 21, entered the service of Dr. N. C. Gilbert, St. Luke's Hospital, on March 6, 1928, because of a painless swelling on both sides of the neck for one and a half years. The swelling on the left side was noticed several weeks after that on the right. There were no other complaints. The condition had been diagnosed Hodgkin's disease, and the patient had received several roentgen treatments. These reduced the size of the masses considerably. The only essentials revealed by the physical examination was a firm, fixed mass and a few hard discrete nodules just below the mandible on both sides of the neck. An examination of the nasopharynx at this time demonstrated no abnormalities. Portions of the masses on both sides of the neck were excised for diagnosis. The histologic examination demonstrated lymphoid tissue extensively ingrown by compact masses of small epithelial cells. The appearance and arrangement of the cells suggested that the primary growth was in the nasopharynx. They did not assume the structure of stratified squamous epithelium, and there was no hornification. Following this, Dr. J. Gordon Wilson examined the nasopharynx and found a small carcinoma in the vault. Histologic examination of the tissues which he removed demonstrated lymphoid tissue extensively invaded by small epithelial cells. The infiltrated cells were in intimate relation with the lymphoid tissue reticulum and lymphocytes, a tissue structure corresponding to descriptions of a lympho-epithelioma.

CASE 3.—A white woman, aged 20, entered the service of Dr. R. B. Preble, St. Luke's Hospital, on Feb. 2, 1931, complaining of pain in the right ear and right side of the face, vertigo and right frontal headaches for five months, and painless bilateral enlargement of the cervical lymph nodes for three weeks. Nothing of importance was found on physical examination, except bilaterally enlarged, painless, discrete, and somewhat fixed superior cervical lymph glands. Roentgen examinations of the cranial sinuses demonstrated obliteration of the right anterior ethmoid and right maxillary sinuses. No abnormalities were found in the nasopharynx. Hodgkin's disease was considered the most probable diagnosis, but for confirmation a right cervical lymph node was excised. This contained metastatic carcinoma considered secondary to a primary growth of the naso-

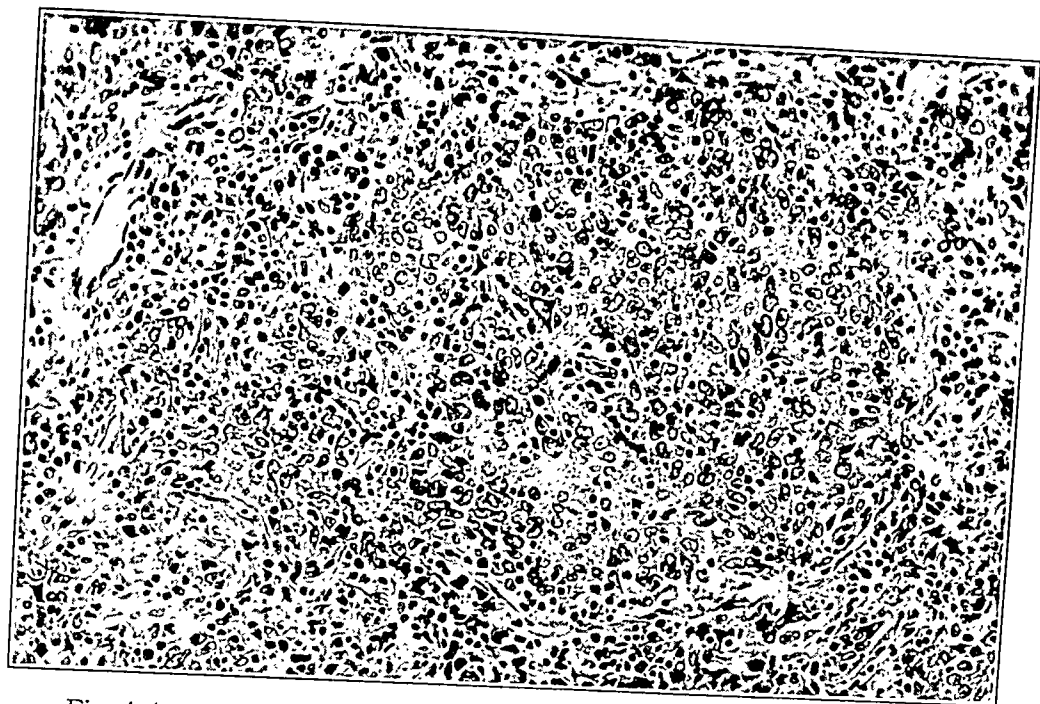


Fig. 4 (case 3).—Photomicrograph illustrating the carcinoma tissues metastatic in a cervical lymph node. The intimate spread of the carcinoma cells into the lymph node is noteworthy. Reduced from a magnification of  $\times 252$ .

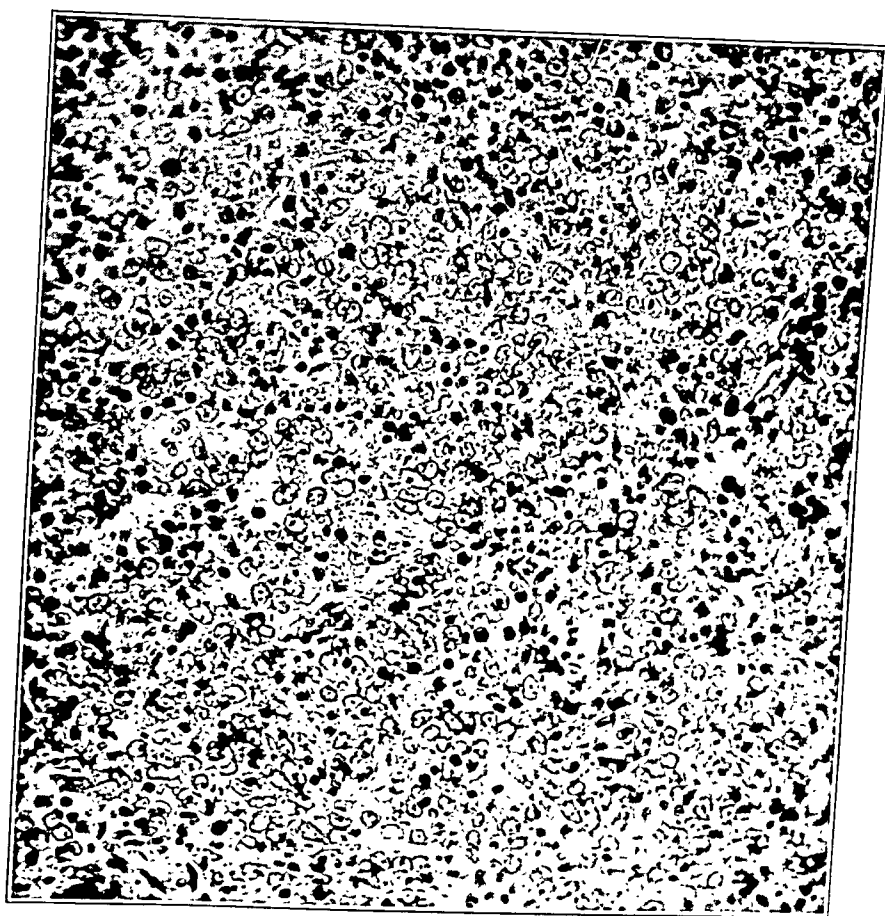


Fig. 5 (case 3).—Photomicrograph of the primary nasopharyngeal carcinoma. Masses of small cells have grown in intimate relation with the lymphoid tissues. The purple quality of the tumor cells in hematoxylin stained preparations contrasts them with the invaded tissues;  $\times 252$ .

pharynx. The lymphoid tissue was markedly ingrown by masses of small epithelial cells with essentially the structure and arrangement of those in the lymph nodes of the second tumor discussed (fig. 4). Dr. J. Gordon Wilson found a cone-shaped carcinoma in the midline of the vault of the posterior nasopharynx. Tissues which he removed contained carcinoma. These had along one edge a regular and narrow squamous epithelial lining. Beneath this was lymphoid and fibrous tissue ingrown by narrow cords and masses of small epithelial cells (fig. 5). They were essentially the same as in the metastases of the cervical lymph glands; they had assumed no definite structure, but were strikingly similar in size and structure to the cells in the basal layer of the lining squamous epithelium.

#### SUMMARY

Three primary nasopharyngeal carcinomas with metastases of the cervical lymph nodes are described grossly and histologically. The diagnosis for each patient was made clinically by examination of surgically excised tissues, and the body of one was examined post mortem. Histologically, all the tumors resembled immature squamous or pseudostratified epithelium, but in one the cells tended markedly to assume the arrangement and structure of squamous epithelium.

An essential clinical feature of these tumors was an insidious and painless bilateral enlargement of the cervical lymph nodes, due to metastases. The bilateral distribution of the metastases resulted from the midline location of the primary growth and the tumor tissue dissemination into the lymphatics on both sides of the neck.

Slight variations in cellular structure occur in these carcinomas, but within the limits of the cell varieties of the pseudostratified epithelium lining the nasopharynx.



# ACTION OF CATHARTICS ON ISOLATED DOG'S COLON

## I. SECRETORY ACTIVITY

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AND

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A review of the literature on the physiology of the large intestine and our own experience indicate that this organ is valuable, although not indispensable to the human economy. One of its interesting functions is the secretion of mucus. In a previous paper, the work of Hay, Luciani,<sup>1</sup> Voit, Carpenter and Goldsworthy and Florey<sup>2</sup> has been mentioned. In an excellent review, along with some work of his own, Heupke<sup>3</sup> summarized the present knowledge of the secretion and excretion of the colon. Using a Thiry-Vella type of fistula in a dog, he found the quantity of secretion from the colon to be rather small; this was not due to resorption of the secreted fluid, because by invagination of the isolated portion in a certain way the material could drop off as it formed. No difference in amount was noted from that ordinarily obtained by irrigating the segment. He found many bacteria in the secretions, even after daily irrigations of the segments for months; so he concluded that no bactericidal capacity was present. The reaction of the secretion was alkaline, with a  $p_{H}$  between 7.5 and 8.4, and it did not change materially following intravenous injection of acids; so that he came to the conclusion that the colon does not function as a regulative organ for the acid-base metabolism of the body, as Leffler has suggested.

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Abridgment of thesis submitted by Dr. Larson to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery. Work done in the division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Luciani, Luigi: Human Physiology, New York, The Macmillan Company, 1913, vol. 2.

2. Florey, Howard: The Secretion of Mucus by the Colon, *Brit. J. Exper. Path.* **11**:348 (Oct.) 1930.

3. Heupke, W.: Ueber die Sekretion und Excretion des Dickdarms. *Ztschr. f. d. ges. exper. Med.* **75**:83, 1931.

## METHOD OF INVESTIGATION

In order to determine, if possible, whether any or all of the various cathartic drugs, when given by mouth, would exert action in an indirect manner, for example, through the blood stream, on the muscle fibers or the nerve endings, we shunted the fecal current around the colons of a number of dogs, by means of the following operation in two stages. The first stage has been described by Mann. Briefly, it was as follows: With aseptic technic and under ether anesthesia, the ileum was sectioned about 6 cm. proximal to its juncture with the cecum, and in most cases from 7 to 10 cm. of ileum proximal to this point was resected in order to remove a portion the blood supply of which tends to be inadequate. The cut end of the distal portion of ileum, usually 5 or 6 cm. in length, was turned in to make a blind end, and the proximal end was left clamped in readiness for anastomosis. The colon was then sectioned close to the rectum, and its proximal end was turned in and replaced in the abdomen. End-to-end anastomosis was then completed between the proximal end of the ileum and the distal portion of the colon, thus reestablishing continuity of the intestinal tract. Through a stab wound in the right lower portion of the abdominal wall, the cecum was brought to the outside, and the main abdominal wound was closed in the usual manner. Twenty-four hours later a cecal stoma was opened through the turned in distal end of the ileum, and a small catheter inserted, a few cubic centimeters of warm saline solution being used to irrigate the proximal portion of the segment.

When the abdominal wound was well healed, usually in from two to three weeks, the second stage was effected by opening the abdomen and bringing the proximal, turned in end of the colon to the outside, and opening it twenty-four hours later, similar to the manner in which the cecum was opened. This left the colon isolated in the abdomen, with the cecum opening to the outside as a fistula on the right, and the colon, near the point where it was sectioned, as a fistula on the left. After healing was complete, a no. 14 or 16 French catheter could easily be passed completely through the segment. The blood and nerve supply, as well as all layers of the bowel, were thus left intact. However, one may question whether the pelvic nerve or the *nervi erigentes* reached the isolated portion of colon. Since, for these experiments, the rectum was sectioned close to the anus, it may be possible that in some instances the motor nerves were interrupted. However, the responses were similar in all experiments, and, furthermore, the normal movements of the intestines imitated closely those of normal large intestines not operated on, as noted by other observers. In one dog, prolapse of from 8 to 10 cm. of colon and ileum took place through the rectum, so that laparotomy and fixation of the bowel were necessary. To avoid this in subsequent operations, instead of the end-to-end anastomosis of ileum to colon, the side-to-side type was done. The latter type of operation seemed, also, to be more free of complications, especially since it gave the advantage of an adequate supply of blood to the line of anastomosis, resulting in less danger of leakage and peritonitis and also of obstruction after operation due to swelling and edema at the lines of suture.

By the oral administration of cathartics, it was determined whether activity took place in the segment of colon that was isolated from the fecal stream. This was studied first from the standpoint of the amount of secretion obtained from the colonic segment by hourly washings with tap water.

Preliminary to the experiments, a no. 14 French soft rubber catheter was inserted through the isolated segment, from the stoma on the right side toward the left (cecum to rectum), and two or three holes were made in the catheter, so that when an irrigating solution was run through it, all portions of the colon

were washed. The ends of the tube were tied together, and the catheter was thus kept in place for from seven to ten days before experiments were carried out; the catheter was allowed to remain in place indefinitely. Immediately after insertion of the catheter large amounts of mucus were secreted, but the amount decreased to the average in from twenty-four to forty-eight hours. Most of the mucus appeared at the distal stoma, although occasionally small globules were present at the cecal opening.

All factors concerned in the experiments were kept as constant as possible. The dogs were made to fast for about twenty hours beforehand, and no food or water was given during the experiment. They were kept on tables most of the time, but were allowed to be up and about, under observation, for ten minutes every two hours. Tap water at body temperature was used to wash the segment. The first washing after beginning the experiment was discarded, for it represented the secretion accumulated over varying periods of time, and when the dogs were left for several weeks with no tubes in the segment, as occurred between the time of the second operations and the running of the experiments, enough mucus would be formed to fill the cavity of the segment completely. This, however, could be easily washed out. The cathartic drug was administered either by stomach tube,

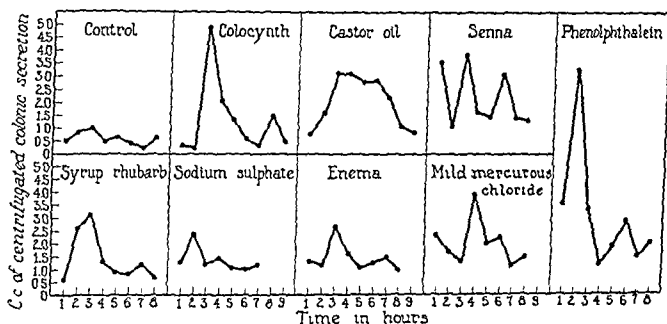


Fig. 1.—Representative amounts of mucus obtained from an isolated segment of colon. In each of the graphs, defecation occurred but once and was concomitant with the peak of each curve, except in the experiments with senna, in which defecation took place three times, owing to a large dose of the drug.

50 cc. of warm water being used as a solvent, or by a 10 cc. gelatin capsule given orally. Whatever the method, the dog received the cathartic immediately after the isolated segment was first washed out. Washings were then made at hourly intervals for eight or nine hours with 50 cc. of water, which was run through the segment three times. Care was taken not to stimulate the colon, either through distention by the fluid washed through it, or by moving the rubber tube any more than was necessary. Outside influences, such as noise and excitement, were kept at a minimum.

Control experiments were carried out in an identical manner. Either a stomach tube was passed and 50 cc. of water given, or an empty gelatin capsule was administered.

The washings were saved in 50 cc. containers, and these were centrifugated at the same speed for five minutes. The supernatant fluid in each container was then poured off, and the remainder was transferred to 15 cc. centrifuge tubes graduated to 0.1 cc. and again centrifugated, all at the same speed, for five minutes. The height in cubic centimeters of colonic secretion was then read, and the results were plotted in the accompanying chart (fig. 1). The dosage of the cathartic

drug was proportional to the weight of the dog, and in most cases was just enough to produce only one or two semiliquid stools within two or three hours. No one animal was purged more than three times a week. Drastic effects from the cathartics were avoided. If the animal showed signs of discomfort on the table before the two hours were over, he was allowed to be up and to defecate if necessary, although care was taken not to permit escape of mucus through either stoma at any time. Naturally, defecation took place more rapidly than normally because of the absence of practically the entire length of the colon, so that its functions of condensing and acting as a reservoir were lost. Observation on the time of action of the cathartics was thus of little value.

#### NORMAL AMOUNT OF SECRETION AND FACTORS INFLUENCING IT

In the control experiments, it was noticed that the level of secretion from the isolated colon of a dog that was lying quietly for several hours at a time was fairly constant, and tended to be less, the more quiet the animal remained. During sleep the level of secretion seemed to be at its lowest, although at no time did the stoma become dry. Following movement of the bowels without a purgative, an increased amount of secretion appeared at the opening on the left side in from ten to fifteen minutes, rarely before. It continued to exude from this opening for about an hour or slightly longer, but was never seen in large globules such as were seen immediately after defecation.

Similar studies were carried out on one animal which became pregnant. Prior to impregnation, the base line of colonic secretion was at a point seemingly lower than it was during gestation; also the rise in amount of secretion during defecation was higher, whether or not this was due to catharsis. Whether this rise is due to an increased vascularity of the pelvic organs, to the irritation and pressure of an enlarged uterus or to other factors is impossible to say.

During an attack of mild diarrhea of unknown origin in one dog, there was also a definite increase in the amount of mucus secreted from the isolated portion of colon. Likewise, when in the course of the diarrhea defecation was induced by catharsis, the rise in the amount of secretion was considerably increased over the normal rise during the naturally induced defecation that accompanied the diarrhea. If the etiology of this attack of diarrhea could have been determined, much might have been learned concerning the overactivity of the isolated segment of bowel during this period. Grossly, the color of the stomas was normal, as was easily seen in a small, everted portion on the left side. However, at regular intervals blanching and reddening of the stump, along with tonic contractions in rings, could be seen during the attack of diarrhea; such phenomena were never noticed at any other time.

EVIDENCES OF ACTION IN THE ISOLATED COLON FOLLOWING ORAL  
ADMINISTRATION OF CATHARTICS

There seemed to be little difference in the subsequent results, whether the cathartic drug was given by stomach tube in 50 cc. of water, or whether it was given by capsule in the dry state, undiluted with water.

Accompanying catharsis induced by drugs such as senna, rhubarb and phenolsulphonphthalein, there was a marked rise in the level of secretion obtained from the isolated segment. No substantial increase in the amount of mucus took place in the segment until defecation occurred, but when the increase took place it was different from that accompanying control experiments.

Castor oil produced the most sustained consistent rise in secretion of any of the cathartics. The increased amount of secretion may possibly be due to marked activity produced in the small bowel by the oil; yet the dogs in this experiment seemed no more uncomfortable than when given other cathartics. Likewise, defecation took place no earlier than with other drugs. It would seem likely that the ricinoleates formed may be absorbed, and possibly some were excreted into the isolated segment of colon; this may explain the tendency for an increased secretion of mucus over a longer period.

Colocynth was selected from the irritant drugs because considerable work has been done on its mode of action. Also, if any absorption of this drug should take place, it would be likely to be manifested by an increase in activity of the isolated portion of bowel, as regards both movements and secretory function. Small doses were used, and in two of three dogs a well sustained rise in secretion from the isolated segment was noted. A large quantity of mucus was present in the stools, which is evidence of the irritative action of the drug. Whether the increased secretion from the colonic segment was due to general discomfort or restlessness, to activity in the small bowel or to absorption and secretion into the isolated bowel is problematic.

The salines produced effects similar to those in control experiments, and, so far as could be determined, enemas of 200 cc. of tap water gave results in no way remarkable.

## COMMENT

In this series of experiments, measurements of action in the isolated segment of colon were based on the amount of secretion which, under various conditions, could be washed out of the segment. The secretion is no doubt composed largely of mucus, but may contain other substances excreted by this route, as evidenced by the studies of Bargen, Osterberg and Mann.<sup>4</sup> The fact that most of the secretion appeared

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4. Bargen, J. A.; Osterberg, A. E., and Mann, F. C.: Absorption and Excretion of Arsenic, Bismuth and Mercury: Experimental Work on the Colon, *Am. J. Physiol.* 89:640 (Aug.) 1929.

at the stoma on the left side can be attributed to peristaltic activity in the segment. However, since the function of the distal part of the colon is that of contraction for the purpose of evacuation of the bowel, one would expect more mucus to be secreted in that segment of the bowel.

Secretions from this isolated segment of colon may be comparable to meconium, because after remaining in the bowel for a considerable time the content became dark and of a putty-like consistence. However, it never became black or pitchy unless exposed to air. Between the time of the final operation and the time when the catheter was inserted through the isolated portion semipermanently, it was found that enough secretion had accumulated to fill the lumen completely. It usually was firm enough in consistence so that it could be washed out en masse. Several of these masses were hardened in formaldehyde,

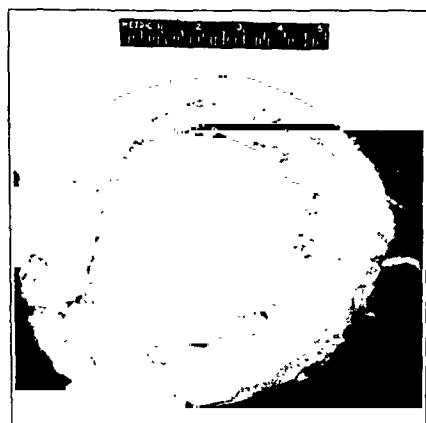


Fig. 2.—Cast of an isolated segment of colon, composed of solidified mucus. It filled the entire lumen and was extracted with considerable difficulty.

and seemed to represent an accurate cast of the isolated segment of bowel (fig. 2). Hurst explained this as coagulation of the mucus, owing to the presence of mucinase, which is secreted by the mucosa of the intestine.

Luciani claimed that most of the nitrogen excreted in the feces originated in the intestinal secretions together with cellular debris from the wall of the bowel, and our observations seem to bear out this contention. Several determinations of the total nitrogen content of the secretion from this isolated segment of colon were made by the Kjeldahl method, and were found to be rather high, varying from 7 to 12 per cent for each specimen, depending on the amount of mucus present, tending to show that a certain amount of nitrogen is excreted in this manner. It may be noted that in so-called mucous colitis, when large quantities of mucus are eliminated, the loss of nitrogen to the body may be enough to contribute to the low resistance of the subject.

It is possible that the increase in intra-abdominal pressure during defecation may mechanically force to the outside the mucus already present in the segment, yet this factor does not seem to account for the entire volume of secretion produced. If the mucus expelled were that already present in the segment before defecation, one would think that it would appear immediately after defecation instead of ten or fifteen minutes later, and also that it would be present only transitorily instead of for an hour or longer. However, it is no doubt true that the movements taking place within the isolated segment of bowel aid in the expulsion of the content.

Attempts were made to interrupt the act of defecation just before the stool was passed, and they were successful in several instances. In each case it was found that the rise in the amount of secretion was only slightly above normal and did not reach the height produced by actual defecation. Furthermore, after vomiting no definite increase could be ascertained, and in a few cases in which several defecations took place in rapid succession following the administration of a drug, the rise was higher than could be accounted for by simple mechanical pressure exerted the same number of times. Again, in a number of instances, depression of the curve below the normal level took place immediately after the height was reached following defecation (fig. 1), and this at first thought might be taken as evidence that mechanical pressure from straining forced most of the secretion from the segment, leaving behind a smaller amount than usual. However, if this were the case, it seems more logical that the depression would occur more uniformly than it did, and that it would be greater and would last considerably longer.

One animal, with prolapse of 8 cm. of the distal part of the colon through the stoma on the left side, offered an excellent opportunity to visualize the amount of secretion at various times. During the time the animal lay quiet on the table, the prolapsed portion of the colon was constantly covered with approximately the same amount of secretion. However, at the time of, and immediately following, defecation definite beads of mucus appeared on this surface, and they could be collected in considerable amounts. Furthermore, when this dog was placed on the table following defecation, a watery, thin, freshly secreted type of mucus ran down the edges of the prolapsed bowel, and in time was replaced by the thicker, tenacious type of secretion.

Finally, as a means of further observation, exteriorization of a segment of colon was effected, in a manner similar to that employed by Drury, Florey and Florey.<sup>5</sup> With the usual aseptic technic and with the animal under ether anesthesia, the large intestine was with-

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5. Drury, A. N.; Florey, H., and Florey, M. E.: *The Vascular Reactions of the Colonic Mucosa of the Dog to Fright*, J. Physiol. **68**:173 (Oct.) 1929.

drawn through a laparotomy wound, and 2 cm. was resected, leaving the mesentery of this segment intact. End-to-end anastomosis of the colon was then effected, the resected portion was brought to the outside through a stab wound, and the abdomen was closed. The exteriorized bowel was then opened longitudinally, and the edges were turned and sutured, with the mucosa outward, into an oval area from which the skin had been removed. After healing was complete the secretions could be observed in this segment of colon, in the absence of the factor of changes in intra-abdominal pressure. It was noted that this patch was always covered with a layer of mucus, and that it showed changes in color such as Drury, Florey and Florey have described. However, on examining the patch for a long time, both before and after defecation, and by carefully absorbing any excess mucus formed with a soft piece of gauze, it was definitely seen that there was an increase at the time of and following evacuation of the bowel. This was not apparent immediately as large globules, but was a slow, gradual process, taking place for a period of from ten to fifteen minutes or longer. These observations would tend to show that there is an increased secretion of mucus during the act of defecation, independent of mechanical pressure exerted by the abdominal musculature.

The function of the mucus secreted at the time of defecation is obviously that of a lubricant to the feces. There is also the probability that, under normal conditions, the mucus-producing goblet cells react directly to the mechanical, or possibly chemical, stimulation of the content of the bowel, so that a nervous reflex is not necessary in the production of the mucus. However, the increased products of mucus present in the isolated, reversed and implanted segment of colon at the time of defecation cannot be explained by a mechanical stimulus within its lumen. Two possibilities present themselves. The first and most likely is that a nervous reflex involves the musculature of the wall of the bowel, throwing it into contraction at the time of defecation and resulting secondarily in stimulation of secretion of its goblet cells. This possibility can be supported on the basis of the histologic structure of the glands of the mucosa. A less likely explanation is that a nervous reflex involves the secretory cells themselves. Florey and others have demonstrated beyond a reasonable doubt that no nerve fibers reach these particular cells, so that this possibility receives little support. Furthermore, the mechanical protection of a viscous layer of mucus over the lining of the bowel is an efficient agent to prevent penetration by bacteria. Also, the more irritating the content of the bowel, the more mucus is poured out, and, consequently, the greater are the chances of protecting the lining of the bowel by the secretion.



Mucus may have some function as a regulator of absorption. In other words, on the right side of the large intestine fluids are continuously being absorbed, and to aid in this process there should be as little mechanical barrier, such as a layer of secretion, as possible. It may be that if persons secrete large amounts of mucus, the excess contributes to the looseness of the stools.

#### POSSIBLE SOURCES OF ERROR IN OUR EXPERIMENTS

1. The objection might be made that functional disuse of the isolated portion of colon is accompanied by atrophy or degeneration of its tissues, which might impair its motor or secretory function. However, this does not seem likely. No specimens were taken for biopsy, yet all layers, as well as the blood and the nerve supply, were apparently intact, and there is no reason to believe that any change from the normal took place. It is true that practically all of the colon was out of the fecal stream, and its condensing and reservoir action was lost, resulting in a greater fluidity of the stool and more frequent defecation, as well as less complete absorption of water and possibly of some foods. Furthermore, the normal stimulus to the colon exerted by the presence of fecal matter was absent, and the amount of secretion may not have been similar to that obtained under normal circumstances. However, with the control experiments for comparison, these objections are apparently not serious.

2. It might be objected that washing the mucus from the isolated portion with a nonsolvent material such as water does not clean the segment completely, owing to the tenacity and adherence of the mucus to the intestinal wall. However, after many trials it was found that when the water was run through the segment three times, only small shreds could be obtained in subsequent immediate washings, so that this source of error would be small and would be the same approximately for each experiment.

3. If mucus is allowed to be exposed to the drying and shrinking effect of air, its volume conceivably might become markedly reduced, so that in a volumetric determination such as that used here the results would not be accurate. This objection was avoided by removing any accumulation of mucus which appeared on the outside between washings into a test tube containing a few cubic centimeters of water. From this standpoint, determination of the total nitrogen in a specimen by the Kjeldahl method might have been more accurate; however, the limits of experimental error were not so closely defined as to make this procedure necessary.

## CONCLUSIONS FROM EXPERIMENTS

1. The colon constantly secretes a certain amount of mucus which at the time of defecation seems to be increased, and this is in harmony with the anatomic and histologic structure of the colon. The function of mucus is that of a lubricant to the feces. It acts as a protecting agent to the lining of the wall of the bowel. It has no appreciable digestive power.

2. Cathartics given orally and enemas given by rectum did not seem to affect the amount or the rate of secretion in a loop of colon that was isolated from the fecal current until defecation took place.

3. During defecation, whether this was due to cathartics or enemas, or whether it was spontaneous, a visible and actual increase in secretion of mucus took place in the isolated segment of large bowel. It did not seem to be due to expulsion of the mucus from this portion by intra-abdominal pressure alone. The production of this increased amount of mucus seemed to be due to the increase of various types of movements of the wall of the colon itself, concomitant with the process of defecation, and these movements seemed to act on the goblet cells in such a manner that mucus was mechanically expelled. There is no evidence that a separate nervous reflex is involved in this secretion.

4. Purgative drugs with drastic action, such as colocynth and castor oil, produced an amount of secretion which was definitely higher at the time of defecation and was prolonged for a greater length of time afterward than any of the other cathartics. This was attributed to the high degree of irritability of the isolated segment of colon, with its consequent long-continued motor activity resulting from the use of these drugs.

5. Two factors which seemed to raise the normal level of secretion were attacks of diarrhea of indeterminate etiology and pregnancy. Likewise, the rise in the amount of secretion in the presence of these conditions, induced by defecation from catharsis, was greater than the usual increase when the dog was in a normal state.

6. By isolating the colon from the fecal current and by exteriorization of portions of the large intestine, questions of secretion, absorption, excretion and resorption in the colon of drugs, metals, salts, dyes and the like could be fairly definitely worked out.

# ACTION OF CATHARTICS ON ISOLATED DOG'S COLON

## II. MOTOR ACTIVITY

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In a previous report<sup>1</sup> experiments relating to the secretory activity of an isolated segment of the dog's colon were considered. This study concerns the motor activity of the isolated colon under the influence of a similar series of drugs.

The movements of the proximal portion of the colon in most animals are both peristaltic and antiperistaltic, and although in man those of the latter type have not been definitely identified, there seems to be no doubt of their presence. Other movements take place here, such as segmentation, serial sectioning, haustral changes, propulsive peristalsis and possibly mass movements, so that the total effect is a thorough mixing, kneading and churning of the content, resulting in conditions facilitating absorption.

### METHOD OF INVESTIGATION

In this study dogs were used, and although it is true, as many observers have stated, that the colon of the dog is distinctly of the type found in carnivorous animals and that it has little or no right segment, possessing movements mainly repressed by those of the distal portion, yet there is the advantage of size and adaptability to experimentation with this animal and there is enough similarity to the colon of man so that results should be fairly conclusive. Likewise, no other laboratory animal can be so easily trained or so satisfactorily operated on as the dog. Furthermore, although the cecum of this animal is very short, it was possible in the experiments which we shall describe to place the balloon in this segment of the isolated organ, thus obtaining records which, at least partially, are comparable with those of animals which have a colon the proximal part of which is long and capacious. What survives of the colon is really the distal portion, the whole length of which can take part in contractile movements, having for their purpose complete evacuation.

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From the Division of Medicine, the Mayo Clinic.

Abridgment of thesis submitted by Dr. Larson to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery. Work done in the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Larson, L. M., and Borgen, J. A.: Action of Cathartics on Isolated Dog's Colon: I. Secretory Activity, *Arch. Surg.*, this issue, p. 1120.

The colon was isolated in a manner identical with that described in the study on secretions. Kymographic tracings were made of the movements taking place in this isolated segment of the colon, by the use of small balloons connected with a water manometer system. Prior to insertion of these balloons, a large, no. 24 French, soft rubber catheter was inserted through the segment and was allowed to remain there for several weeks before the experiments were started, and likewise between experiments this catheter was kept in place in the isolated segment. Because the rubber tube was approximately the same size as the balloon system used, it had an effect similar to that of the distending force being constantly present, thus accustoming the colonic segment to this type of foreign body and tending to make its movements on balloons as nearly normal as possible. To correlate activities in the distal and proximal portions of the large intestine, a set of three balloons was used: one in the most distal segment, another in the most proximal segment and a third midway between the other two.

Female dogs were selected for use, mainly because they are much more easily trained to lie quietly for long periods than are males. In some instances, continuous recordings were made over a period of from eight to ten hours, so that the capacity of an animal to be trained was a factor of importance. After the lapse of a few weeks the animal would defecate on a specially prepared table without disturbing the recording apparatus and without moving about, so that tracings were obtained before, during and after the act under normal or nearly normal conditions. Similarly, keeping the large catheter in place before and between experiments aided in accustoming the bowel to the balloons and reduced to a minimum any tendency to abnormal reactions. Another factor of distinct advantage in this preparation, which made for the maintenance of normal conditions, was the accessibility of the segment without previous cleansing or irrigations such as would be necessary in using the colon through which the fecal current was passing. Preliminary manipulation was found to have a definite influence in the stimulation of movements, as could easily be demonstrated in the isolated segment of the colon by irrigations prior to experimentation.

#### FINDINGS AND RESULTS IN THIS SERIES OF EXPERIMENTS

In recording movements in the isolated segment of the large intestine, care was taken that the balloons each time should be in precisely the same place. This was especially important regarding the proximal portion, where the cecum is extremely short so that with only small displacements the balloon might be pushed through into the colon beyond and what little cecum the dog has would not be utilized. The contractions in the cecal segment were found to be considerably different in character from those of the other portions of the large intestine from which records were made.

*Types of Movements.*—Movements in the proximal, or cecal, segment of the colon can be divided into three types, as illustrated in the accompanying tracings. First are the large tonic waves, variable in amplitude and duration, but ordinarily appearing from six to eight times an hour and lasting for about five minutes. These could be elicited at any time by sufficient distention (overdistention) of the cecal balloon (fig. 1), when they appeared in most rapid succession

and reached the highest level. These large tonic waves frequently slowed down during sleeping or after fasting, but as a rule they were remarkably regular and even and were little influenced by outside factors. Surmounting the large tonic waves was a smaller, similar type of movement, designated as small tonic waves. These represented a more rapid type of movement, with a rate of from five to six in four minutes, and comparable in time, contour and duration to motions in the distal segment. This type of wave was well illustrated in the experiments with mild mercurous chloride and senna, in which considerable stimulation of movements took place. Superimposed on the small tonic waves were short, rapid contractions, appearing from eight

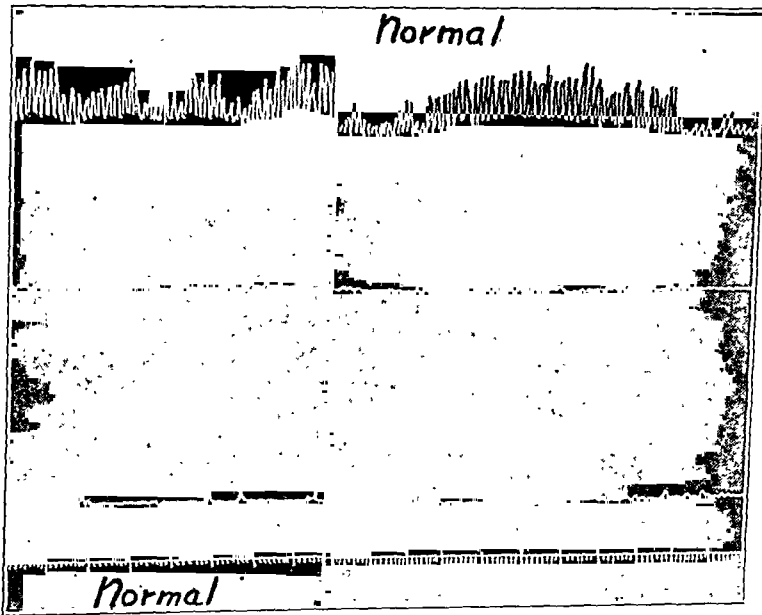


Fig. 1.—Tonic waves of the cecum and normal quiescence of the middle and distal parts of the colon.

to ten times a minute. These movements were almost always present, were markedly uniform in amplitude and duration and apparently were seldom transmitted to the distal parts. Even with marked stimulation of the cecum, in which high tonic waves were elicited, no activity of consequence could be initiated in the distal portions of the segment. These small contractions, in fact, seemed to be the only movements that were normally present in the colon, except during the act of defecation, when the entire organ participated in evacuating its content. These small contractions may be concerned in the mixing and churning function of the cecum, and may or may not be antiperistaltic. This point is considered elsewhere in this paper.

Activity transmitted by the middle and distal balloons was distinctly similar in character and to a certain degree was classifiable as in the proximal or cecal segment. In this series of experiments it was noted that the distal portion of the colon was normally almost completely quiescent (fig. 1); only small, almost unnoticeable movements were present, and these were similar, as transmitted by the two distal balloons. Activity resembling that recorded by other authors took place only after stimulation, such as overdistention of that region, various reflexes and defecations. Overdistention of the segment of bowel by slightly raising the pressure within the distal balloons resulted in a stimulation of movements. These movements continued to a variable extent, depending on the strength of the stimulus, but the greater the stimulus, as a rule, the more irregular the movements. Activity of

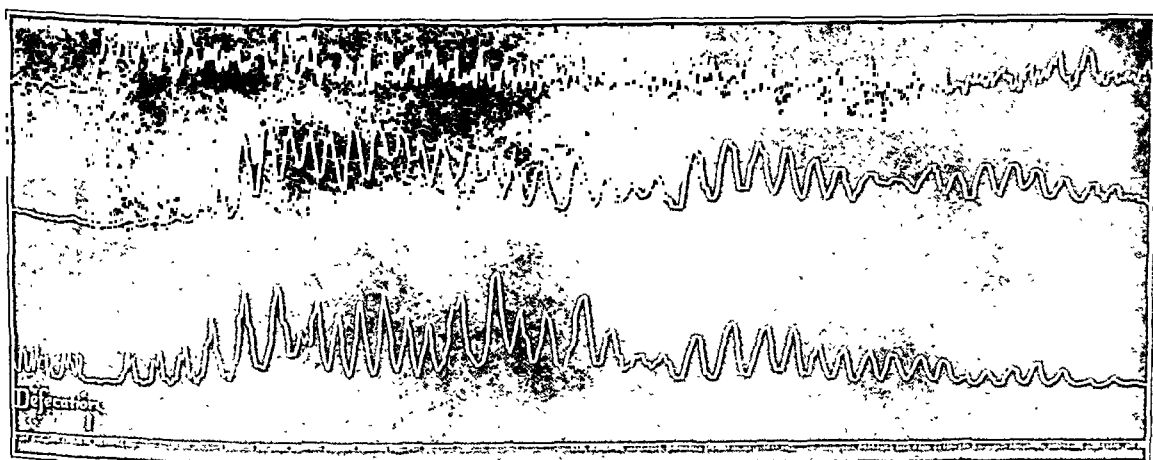


Fig. 2.—Activity following the administration of syrup of rhubarb. It continued for slightly longer than the normal time (i. e., from twenty to thirty minutes elapsed before the middle and distal portions returned to normal).

the proximal part of the colon extended into the distal part only at rare intervals, and then it could be progressively followed through the middle part to the distal part, with a definite delay before reaching the latter. The delay was not present so much during normal processes as it was after catharsis such as that caused by colocynth and syrup of rhubarb (fig. 2). After defecation a definite delay could be noted in the anally directed movement. No such delay could be demonstrated in waves going in an opposite direction; in other words, orally directed or antiperistaltic movements could not be definitely proved to be present. Changes in tonus in the distal segments, unlike those in the proximal segments, were less frequently seen and were less pronounced, although they appeared fairly constantly after stimulation of this region.

The principal movements in the distal parts of the isolated segment of the colon were rather high tonic contractions, coming at a rate of from five to six in four minutes, but not necessarily related to or timed with the waves of a similar type in the proximal segment. These were more frequently transmitted from the middle balloon than from the more distal one; in the more proximal region they were initiated with greater ease and continued a little longer after they were started than in the distal region. From this it would seem that the irritability, or the gradient, is higher more proximally in the colon. It was also noticed that large changes in tonus in the middle and distal segments seemed to represent a higher degree of irritability than the small changes in tonus alone, for the distal balloon never became quiet until all large tonic waves had disappeared for some time from the middle segment. This seemed especially true when stimulation of movements had been induced by catharsis. As in the proximal segment, small, rapid contractions were likewise present during periods of activity of the entire large bowel. It could not be determined accurately whether these had been transmitted from the proximal segment, although the evidence seems to point against this, as the movements were independent and localized to the region from which recordings were made.

The most common type of movement found in the colon of the dog is no doubt a pulsating type of wave in which the entire organ contracts systolically as a single unit. This seemed to be the usual type of activity present. It was less frequently seen when irritability of the large intestine was increased by the administration of cathartics. With the use of the latter, a peristaltic type of movement was usually elicited, and no doubt had its purpose in the attempt at elimination of the drug. However, even during the normal response to stimulation in which systolic pulsations resulted, there frequently were transitions of this type of movement into the peristaltic waves. In the pulsating type of movement, the cecal portion of the colon rarely took part, continuing with its usual rapid type of activity and being influenced very little by happenings elsewhere.

The waves which were peristaltic in nature and which apparently were transmitted through the colon were mostly the small, tonic contractions surmounting the large tonic changes. They could be followed through all three balloons, with a delay of from ten to fifteen seconds between each two waves. These waves were most frequently directed anally, but at times it seemed as though a few traveled orally, although this could not be definitely established. It is rather unlikely that reverse waves ever really appeared.

The small, rapid waves of the cecum were frequently simultaneous with similar contractions in the other parts, and they could not be

seen to be transmitted with a delay analward; in other words, these waves also occurred as pulsations of the entire organ. Their rate on the average was five or six to one wave in the middle or distal part, and it may be that summation of these contractions is responsible for the changes in tonus in the distal parts. If this is the case, it would be difficult to classify these movements as peristaltic; more likely they are the result of a local stimulus or of the summation of the smaller movements. It is no doubt true that many of these waves were entirely localized, having no effect on, and not being affected by, movements in other parts of the colon. Frequently, an inhibition in tonus was present, and was most marked in the balloon nearest the distal opening of the colon, apparently jumping the middle portion. Occasionally it was noted that during periods of activity of all parts of the isolated segment contractions in one part seemed frequently to be associated with depressions in tonus in another part, and this at times suggested a true inhibition, but the relation to peristalsis was not always uniform regarding time and amplitude.

Contractions in the distal part of the colon of the dog apparently bear considerable similarity to those of the corresponding segment in the colon of man, according to studies made by Hines, Lueth and Ivy.<sup>2</sup> These investigators inserted balloons into the sigmoid flexure and rectum in normal and in constipated persons, and obtained tracings which are almost identical with those recorded from the middle and distal parts in our study.

*The Gastrocolic Reflex.*—The distal part of the colon, as has been explained, is most frequently quiet, becoming active usually only when stimulated by various reflexes, distention and the like. Occasionally a tonic wave in the cecum will progress anally far enough so that a peristaltic type of movement traverses the colon, but much more frequently the movements of the two sides are independent of each other. In the present study, one of the easiest methods of producing active movements in the distal part of the isolated segment of the bowel was to elicit the so-called gastrocolic reflex. This was best accomplished after causing the animal to fast for about twenty-four hours and at a time when the bowel was likely to be full of feces. At the time of its usual feeding, the dog was given a portion of fresh meat, and invariably the results were as follows: Within one or two minutes the tonus of the cecum fell considerably, and its movements became almost completely diminished for a period of two minutes; then they reappeared with slightly increased force and amplitude. At about the same time, the

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2. Hines, L. E.; Lueth, H. C., and Ivy, A. C.: Motility of the Rectum in Normal and in Constipated Subjects, *Arch. Int. Med.* 44:147 (July) 1929.



tonus of the middle part became elevated, and was accompanied by small, rapid, superimposed contractions. In another sixty to ninety seconds, short, rapid waves were transmitted from the most distal balloon, and these were superimposed on small changes in tonus, which became increasingly greater in amplitude and were finally recorded as large, strong contractions. These movements in the middle and distal parts then slowly diminished until the colon became perfectly quiet, in the same order as they had appeared, the whole process taking from fifteen to twenty minutes. It was noted that usually the most distal balloon was the slowest to become active, but its contractions were considerably stronger after once becoming started (fig. 3).

*Defecation.*—Striking differences in colonic motor activity were found between the normal act of defecation and that following the use

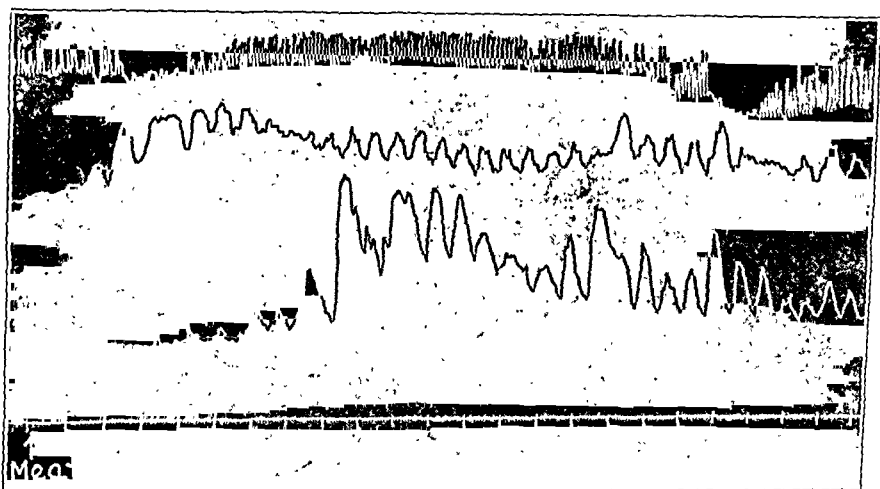


Fig. 3.—Initiation of activity in the middle and distal segments of the colon, lasting from twenty to twenty-five minutes, a rise in tonus of the cecum and greater irritability of the middle than of the distal portion.

of drugs. In defecation, as it took place normally, the cecal and distal parts of the isolated segment of the large intestine were in their customary state of activity, consisting of small, rapid contractions in the cecum, with changes in tonus, accompanied by practically no activity in the parts where the two distal balloons lay. That is, the isolated segment did not seem to take part in the act of evacuation. However, when the dog began to strain, the tonus of the cecum usually rose considerably (fig. 4), and practically always its movements stopped until straining ceased (until defecation was completed). Activity continued in the distal part for variable lengths of time, but in the normal response for not more than from fifteen to twenty minutes, while the cecum went on with its usual contractions. Generally, slowing of activity was

first noticeable in the record made by the most distal balloon, and this was likewise true in the case of the disappearance of tonic waves, with those in the cecum noticeable the longest. Many attempts were made by abdominal pressure, in most cases exerted longer and with greater force than is occasioned by defecation, to elicit a response similar to that just described accompanying defecation, but each attempt was unsuccessful.

The salines, magnesium or sodium sulphate, given in the same manner and with the same dosage as described for the experiments on the secretory mechanism of the colon, produced results which resembled the normal process more closely than did those of any of the other

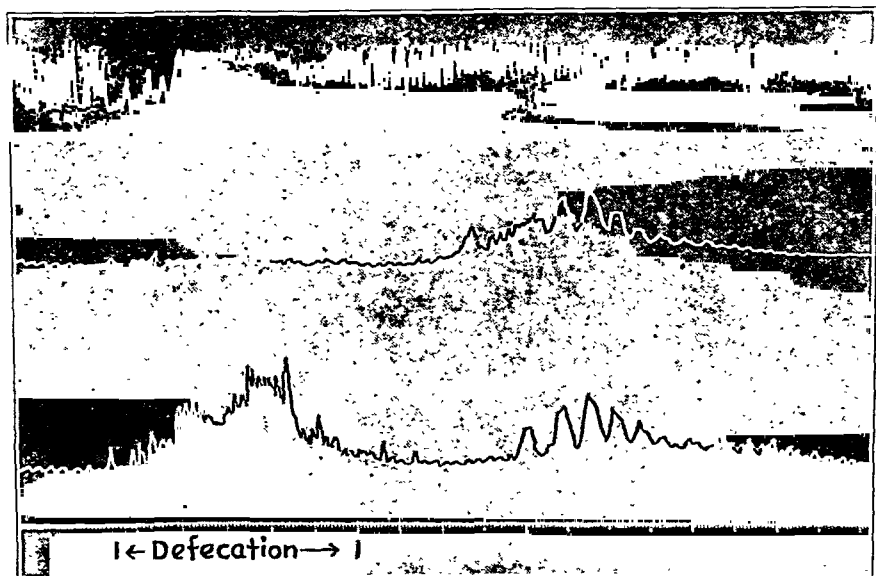


Fig. 4.—With straining incident to defecation, a considerable rise in tonus is recorded by the distal balloon. Activity in the isolated loop is first noted in the middle segment and then in the distal segment, but it does not last more than from five to seven minutes.

cathartics. The outstanding variation from the usual type of activity with spontaneous defecation was the increased length of activity in the distal and middle parts of the isolated segment of the colon. With the saline laxatives this activity lasted for from eighteen to twenty-eight minutes, rarely any longer, before complete quiescence was resumed. Phenolphthalein falls in a similar class, continuation of movement in the isolated colon taking place for from twenty to thirty minutes: with syrup of rhubarb (fig. 2), the reaction was not much different, requiring from twenty-four to thirty minutes for a return to normal. Mild mercurous chloride and senna were longer in their action, and it took

from seventy-five to ninety-five and from fifty-five to seventy minutes, respectively, for a complete return to a quiescent state. Lastly, castor oil and colocynth (fig. 5) apparently had points in common. After the administration of castor oil, it was found that many hours were required before the activity in the segment quieted down enough to be classed as normal, and even twenty-four hours later the increased irritability was present. Apparently nothing would quiet the segment until elimination of the drug had taken place. Forty-eight hours after defecation, however, the segment returned uniformly to a normal state of quiescence. The irritant action of colocynth was even more pronounced; it was not until three days after the administration of the cathartic that the distal portion of the segment regained a normal state. Colocynth also produced a characteristic reaction immediately after defecation, consisting

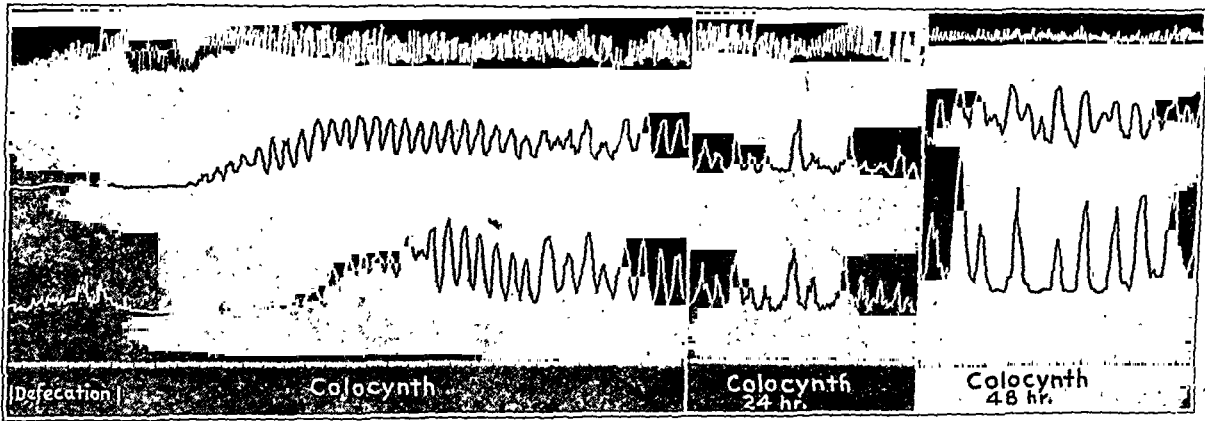


Fig. 5.—Long-continued activity following the use of the irritating drug colocynth. Even forty-eight hours was an insufficient time for the segment to return to a normal state.

in a marked elevation of tonus in the two distal portions of the segment of the colon, accompanied by large waves which continued for a considerable length of time. This was entirely different from the after-results of other cathartics, and no doubt demonstrated the increased irritability produced by this drug.

It was found that after the rectal injection of tap water in quantities of from 100 to 150 cc. defecation was followed by approximately the same type and length of activity as that resulting from normal emptying of the bowel. Complete cessation of activity in the cecum attended insertion of the catheter through the anus. The cecum remained quiet until the tube was removed; then movements were resumed, similar to those which had been present before they had been stopped. Rectal distention by means of balloons, using 15 cc. of air,

was accompanied by the same results. Sometimes a lapse of sixty seconds or more took place before contractions reappeared, but when they reappeared, they seemed to be just the same as they were when they left off, no change having taken place during the interruption. This is in agreement with recent work by Lawson and Templeton,<sup>3</sup> who studied the effect of raising the pressure in various parts of the colon on the movements elsewhere in that organ. They obtained definite depression in tonus and activity in the proximal part of the colon when balloons were inserted into the distal part, and this is represented by kymographic tracings which are almost identical with those found in the present study (fig. 5).

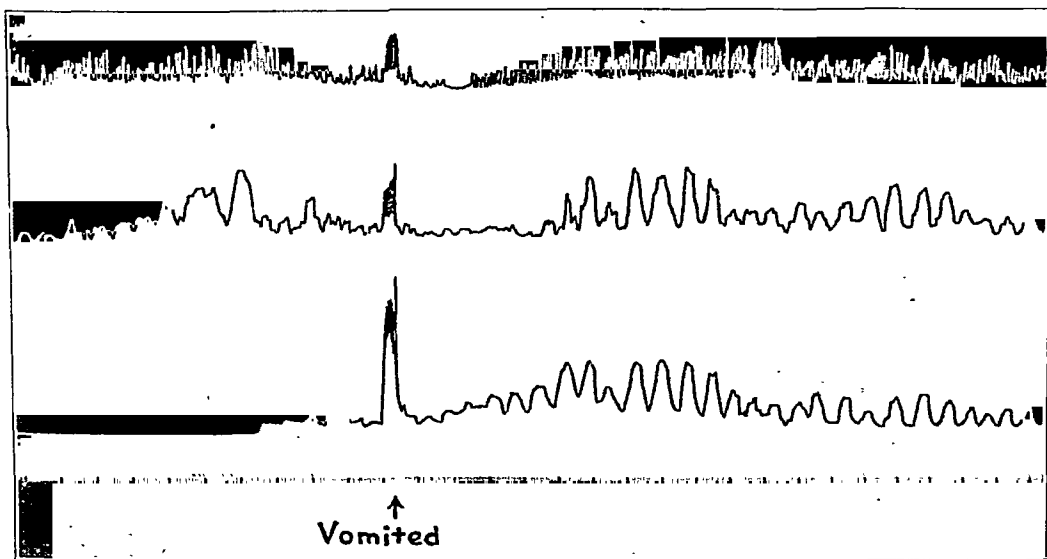


Fig. 6.—Effect of vomiting on the isolated segment of the colon. Apparently there was some activity (reverse peristalsis) in the middle portion of the segment, preceding vomiting. There was considerable stimulation of movement after vomiting.

A study of the gastrocolic reflex under the influence of laxatives showed that the reflex was most marked and lasted longest several hours after a cathartic had been given, but before defecation had taken place. This was especially true after the use of irritant drugs such as castor oil and colocynth, and was less after the others (fig. 2). After defecation there was seldom much of a response with the ingestion of food

3. Lawson, H., and Templeton, R. D.: Studies in Motor Activity of the Large Intestine: Influence of Balloon Technique Upon Colonic Mobility, *Am. J. Physiol.* 99:87 (Dec.) 1931.

until about twenty-four hours later, and then it was elicited with its usual intensity. It would seem from this evidence that the bowel responds best when it is full of fecal material.

Various other stimuli were applied to the isolated segment of the large intestine. The injection of 50 cc. of ice water into the middle of the loop over a period of two minutes by means of the arrangement described, without disturbing the balloons, resulted first in a fall of

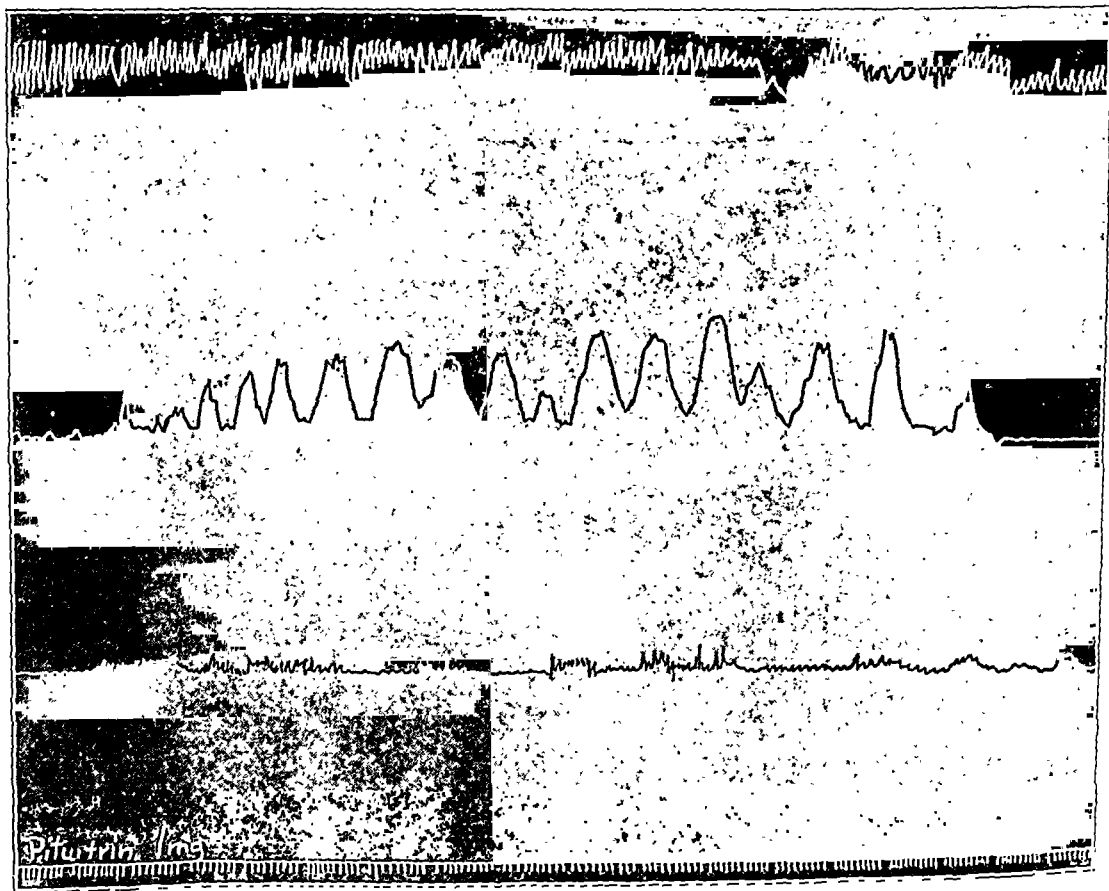


Fig. 7.—Effect of the subcutaneous injection of 1 mg. of solution of pituitary on an isolated segment of the colon. There was mild stimulation of movements in the middle portion, but little change in the distal portion.

tonus with cessation of the movements of the cecum (fig. 6). This was followed shortly by fairly large and rapid tonic waves in the cecum, with superimposed rapid contractions, and also by movements of moderate amplitude in the middle segments. In the distal balloon, no movements appeared, indicating lessened irritability in the portion and demonstrating that the threshold for activity had not been reached. The effect of cold on the colon in these experiments demonstrates the

difficulty in using solutions of low temperature for enemas. Because of the distress caused, very small amounts can be injected and very little can be retained, whereas much larger amounts can be utilized if the solution is warm, as illustrated in the following experiments. Fifty cubic centimeters of warm water (44 C.), injected similarly, had a definitely relaxing and sedative effect, which was noted by a fall of tonus in the cecum and by cessation of movement in the various parts.

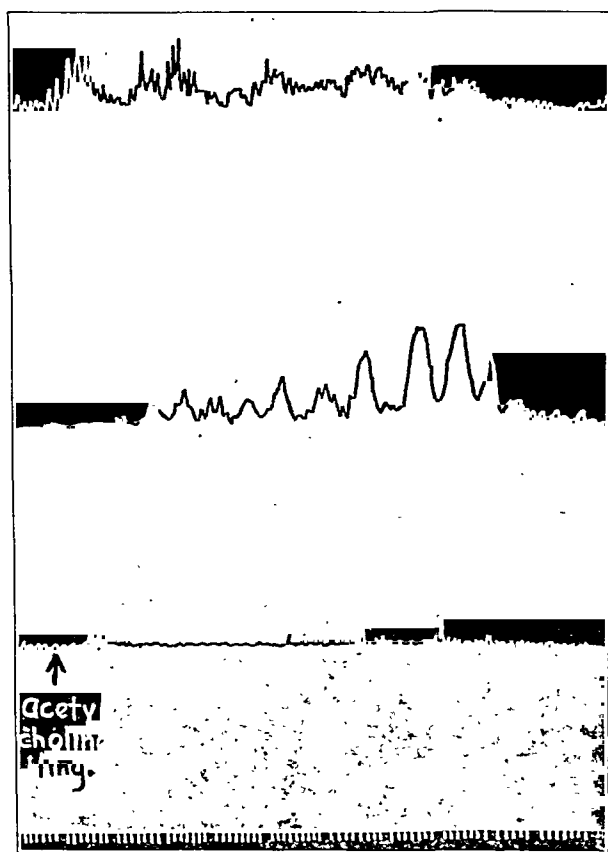


Fig. 8.—Subcutaneous injection of 1 mg. of acetylcholine had an effect somewhat less than that of solution of pituitary but similar to it.

Tap water at body temperature, no matter how long or how much was injected without producing distention, seemed to have no effect on the movements in any portion of the loop.

Movements could, of course, be stimulated readily by mechanical means, such as pinching and pricking.

To determine the effect of psychic stimulation, if any, on the movements of the large intestine, such as is often said to follow fright and

other emotions, a cat was suddenly dropped on the dog while the latter was asleep. Some struggling ensued, and soon movements appeared in the middle portion, but no sign of activity appeared as a rule in the distal portion. The cecal contractions continued as previously.

Several drugs were used in attempts to stimulate activity in the isolated segment of the large intestine. Solutions of pituitary and acetylcholine, given subcutaneously, increased the activity in the middle portion to a moderate degree, but had little or no effect in the distal portion. On the other hand, an aqueous solution of 20 per cent sodium

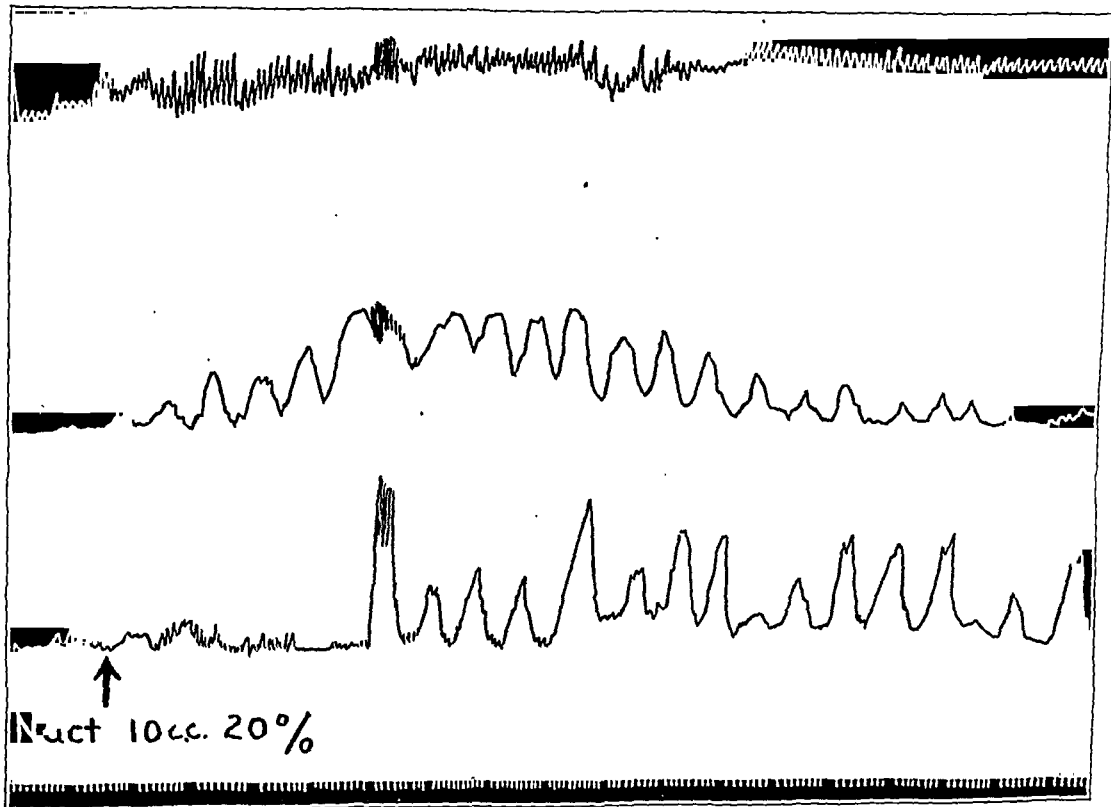


Fig. 9.—Intravenous injection of 10 cc. of a 20 per cent solution of sodium chloride resulted in a stimulation of movements greater than that with solution of pituitary or with acetylcholine. These movements were especially marked in the distal portion of the colon.

chloride markedly increased the movements in both distal balloons (figs. 7, 8 and 9).

#### COMMENT

An isolated segment of the colon is anatomically and functionally like the normal colon. This has been demonstrated not only by observation of the living isolated viscus, but by careful gross and histologic study of the exteriorized organ after death.

The marked difference in activity of the cecum and of the rest of the colon is striking. The cecum seems constantly active, with mixing and churning, probably for the important function of absorption. Besides this, the cecum by its activity tends to retain its content until the consistence of the feces is such that the mass will acquire form. In the distal part of the colon, the most frequent movements are systolic pulsations and not peristaltic waves, and the relation of this to its almost complete inactivity is noteworthy. The chief function of the distal portion seems to be propulsion of the fecal content toward the rectum.

Two possibilities concerning the nature of impulses stimulating activity in the colon during feeding present themselves: 1. A hormone of the gastric mucosa liberated by feeding may stimulate the colon through a humoral mechanism. The shortness of time between feeding and the colonic activity would make this unlikely. 2. Impulses may be transmitted over the mesenteric nerves. This, which was suggested by Alvarez,<sup>4</sup> is the more likely explanation.

Probably the best explanation for activity appearing in the isolated segment of the colon after defecation, instead of simultaneously with it, or even beforehand, rests on the idea of a gradient as conceived by Alvarez and Starkweather.<sup>5</sup> In the process of evacuation of the colon, the gradient of irritability of the lower end (anal) is steepened, and therefore its susceptibility to stimuli is increased. Before defecation there were no movements in the two distal balloons, but after evacuation of the bowel, the gradient of irritability was raised, so that the threshold for stimulation was lowered and the balloons were sufficiently large to stimulate the segment of the bowel into activity. Further substantiation of this explanation can be found in the fact that in the presence of a gradient the most distal part of the colon would be the least irritable, and this was true. On injection of hot or cold water into this segment, the greatest effect was on the cecum, less on the middle portion and the least on the most distal portion. This was similarly true concerning the effect of psychic stimulation. This explanation also accounts for the variable lengths of time during which the cathartics stimulated the isolated segment of the colon. In normal defecation, in which the gradient after the act was immediately returned to its usual level and the threshold was again raised so that movement ceased, this actually seemed to be the case, because activity continued for a much shorter time than following the use of any of the cathartics. Enemas of tap water and the saline purgatives, which are known to have little

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4. Alvarez, W. C.: *The Mechanics of the Digestive Tract*, ed. 2, New York, Paul B. Hoeber, Inc., 1928.

5. Alvarez, W. C., and Starkweather, Esther: XVII. The Metabolic Gradient Underlying Colonic Peristalsis, *Am. J. Physiol.* **47**:293 (Dec.) 1918.



or no irritative action, produced the least amount of activity of any of the drugs. With the slightly more irritant cathartics, such as syrup of rhubarb and phenolphthalein, the activity produced was of longer duration, and with mild mercurous chloride and senna the effects were still more prolonged. When colocynth and castor oil were used, the activity continued for as long as three days, indicating that these drugs may cause generalized irritability of the entire gastro-intestinal tract.

Increased motor activity of the colon seemed to be intimately related to increased secretion of mucus, suggesting that irritants such as we used in these experiments either stimulated both motor and secretory mechanisms alike or acted on a single mechanism controlling both of these functions.

#### SUMMARY

Studies were made on the isolated colons of dogs. The operation to isolate the segment was performed in two stages, and complete healing was allowed to take place, thus making possible observations of conditions which closely approached the normal, because no anesthesia was necessary and operative trauma was not present. It was found that the most common motor activity of dog's colon consists in continued rapid contractions of the cecum at the rate of from eight to ten a minute and systolic pulsations of the distal portion at the rate of about six in each four minutes. However, the latter segment was usually found to be quiet, except during and following defecation, vomiting and reflex stimulation. Respiration did not seem to influence the movements. Even the small cecum in the dog seems to have some function. At times a peristaltic type of movement was noted, but this was present only after catharsis, and seemed to represent an attempt to eliminate the drug. There is definite evidence of a gradient in the production of movements such as those brought on with psychic, thermal or other stimulation. When movements were initiated they were greatest and most easily brought on in the cecum, less easily in the middle portion of the colon and least easily in the distal portion. Likewise, the cecum contracted normally at a relatively rapid rate; the middle portion, less actively, and the distal segment with the slowest action. This was also true in the effect of catharsis; the distal portion continued to be motile for the shortest time, and the cecum for the longest.

The gastrocolic reflex, better called the feeding or appetite reflex, was easily demonstrated and probably takes place through the mesenteric nerves. It depends to a certain extent on an adequate bulk in the colon and on an empty stomach. In man, this reflex is commonly absent, and this may be of etiologic significance in chronic constipation.

In a similar manner, receptive relaxation of the large intestine takes place after feeding, and, as a corollary, early emptying of the stomach favors early evacuation of the ileum and thus indirectly influences the emptying of the colon. These various reflexes indicate a delicately balanced mechanism resulting from reciprocal innervation throughout the digestive tract. External and internal factors, such as drugs and chemicals, mechanical, thermal and electric stimuli, various reflexes and nerve centers demonstrate a high degree of dependence of the alimentary system not only on its own functions, but on the entire bodily mechanism as well.

# A REVIEW OF UROLOGIC SURGERY

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## KIDNEY

*Invasion by Fat.*—Young<sup>1</sup> described 11 cases of invasion of the kidney by fat, or replacement lipoma. In the first case, invasion by fat occurred in the absence of infection, pyuria and nephrolithiasis. In all cases there was an increase in perirenal fat, which was firmer than normal and surrounded the pelvis, entering the hilus around the vessels and pelvis and following the infundibula into the kidney. The pelvis was always embedded in fat, and in some cases was completely obliterated. In 2 cases, not associated with lithiasis, atrophy of the kidney had progressed to a remarkable degree. In the other cases, atrophy of the renal substance had occurred around the fatty replacement.

Young stated that replacement lipomatosis is related to the process commonly known as autonephrectomy. Most extensive fatty invasion has occurred in completely obstructed kidneys. Atrophy of renal substance might be secondary to replacement by fat and cutting off of blood supply. Replacement lipomatosis is important clinically because the condition has been mistaken for renal neoplasm.

Young stated that true renal lipomas are rare, and usually are small and yellowish. They are found as encapsulated nodules, in the cortical layer. They result from rests of fatty tissue which have become included in the kidney during embryonal life. Replacement lipomatosis possesses none of these characteristics.

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1. Young, H. H.: Lipomatosis or Destructive Fat Replacement of the Renal Cortex, Tr. Am. A. Genito-Urin. Surgeons 25:105, 1932.

Gridnev<sup>2</sup> stated that the formation of a fatty tumor in place of the renal parenchyma is of rare occurrence. He was able to find reports of only 39 cases in the literature. He reported the case of a man, 48 years of age, who had had fever of three months' duration. Two weeks before Gridnev saw him, the man had noted a painful swelling in the left flank. The urine was very cloudy. The patient was fat, and the swelling was painful. Without cystoscopic study, a diagnosis of pyonephrosis was made, and transabdominal nephrectomy was carried out. The tissue weighed 800 Gm. and measured 11 by 17 cm. On cross-section, the remains of calculous pyonephrosis, completely set in fat, were found. The case proved to be one of replacement lipomatosis.

Gridnev stated that the perirenal fat occurs in three formations in these types of cases: First, the fat pushes into the kidney through the hilus, so that the pelvis is covered with fat and the fatty tissues penetrate between the columns of Bertini and gradually replace the parenchyma; second, this form, which embraces most of the reported cases, originates through the concentric formation of the fatty capsule, and takes the place of the destroyed parenchyma; third, in this group the renal parenchyma is pressed on from within as well as from without. All these formations eventually lead to complete replacement of the kidney by fat. The present theory as to pathogenesis is that the fatty change of the kidney and intense renal infection, with concurrent atrophy, are simultaneous. However, the real reason for the fatty replacement is still unknown.

[COMPILERS' NOTE.—Replacement of the renal parenchyma by fat is rare. This substitution had been variously designated in the literature as lipomatous nephritis, lipomatous paranephritis, lipoma diffusum renis, lipomatosis renis, fatty transformation of the kidney, fat replacement of the kidney and fatty degeneration of the kidney. These terms are more descriptive of the stages of the pathologic anatomic process in which the entire parenchyma of the kidney may have disappeared. In the earlier stages in which the changes have not as yet occurred in the hilus and polar regions of the kidney, the term lipomatous paranephritis is considered more descriptive. The condition is usually classified with the various forms of paranephritis. The fat may either surround the kidney or limit itself to individual portions. It may even involve the ureter, assuming huge proportions. The replacement by fat usually parallels the renal process of atrophy.

Kutzmann reported 33 cases and suggested the term "replacement lipomatosis." He noted that there are essentially two groups of observers as to pathogenesis; a minority considers that the primary

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2. Gridnev, A.: Ein Fall von sogenannter Fettumwandlung der Niere. Ztschr. f. Urol. 35:180, 1932.

growth arises from the fatty capsule, while coincidentally the fat of the hilus forces its way into the kidney, causing secondary atrophy. The majority, however, hold that the replacement by fat is secondary, and that the atrophy is of primary importance. To support the latter view, it has been pointed out that at times retroperitoneal lipomas assume huge proportions, surrounding and pressing the kidney on all sides and yet causing no destruction or atrophy of the renal parenchyma. If the fatty growth were of a primary nature, histologic examination should reveal traces of renal tissue, but this has never occurred. Between the fatty tissue and the remaining atrophic parenchyma there is usually sharp division. Calculous disease and especially infection appear to be the important factors. Analysis has disclosed calculous disease in 80 per cent of cases. The end-result is usually pyonephrosis. The presence of calculi and the chronicity of the infection may result in proliferative and invasive power of the already hyperplastic peripelvic fat above the renal hilus and invasion around the large vessels. Treatment is directed to the associated pathologic changes and is usually nephrectomy. The replacement by fat usually remains undiagnosed until pathologic examination, since there are no pathognomonic findings. The kidneys in these cases are generally painful, badly infected and functionless.]

*Sequelae by Stone.*—Scholl<sup>3</sup> stated that if renal stones are not removed, secondary infection, urinary obstruction and destruction of the renal parenchyma are not unusual. But another element, not so generally known or recognized, may also enter into the consideration of operation in these cases; that is, prevention of carcinoma.

There is a definite connection between gallstones and carcinoma of the gallbladder, and this same association also appears to hold true in regard to renal stone and certain types of malignant tumors of the kidney, especially squamous cell tumors. Not infrequently, in cases of renal tumor, the history suggestive of malignancy is of comparatively short duration, whereas symptoms of stones or infection have been present for many years. In a large percentage of cases of squamous cell tumor of the kidney there is a long-standing history of trauma and infection; at times the early history suggests the formation of stones.

Scholl explained that definite symptoms suggestive of this type of growth are lacking. Bleeding is comparatively rare, the growths differing in this respect from papillary growths of the renal pelvis. In some cases distention of the renal pelvis and the size of the tumor are amazing, usually the result of gradual, slow occlusion which often is almost

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3. Scholl, A. J.: Squamous Cell Tumors of the Kidney Associated with Stone, *Tr. Am. A. Genito-Urin. Surgeons* 25:51, 1932.

painless. At times the pain which the patient has had intermittently for years increases and is more persistent, or it becomes constant, or there is a change in the pathologic conditions present. Once a change has occurred, the outlook for the patient is very poor.

Scholl reported 2 cases; the patients were both women, with long histories of renal symptoms of long standing. In both cases the cancer was of such a rapidly growing malignant type that it is improbable that it was present for more than a relatively short time. In the first case the author found the stone associated with the squamous carcinoma, and he thought that possibly they were the causes of the cancer. It was obviously impossible to state at what time the cancer started. In the majority of cases reported, stones have been present for a long time, probably long before the onset of the malignancy; early removal of these stones might have prevented or retarded the growth.

Comparison of the excellent results, the simplicity of the operation, and the low operative mortality following removal of renal stones, with the rapidly fatal outcome after the development of a secondary tumor, justify the author in suggesting that renal stones should be removed as early as possible; this is not only because it relieves pain and prevents destruction of the kidney, but also because in some cases, such as those described, it prevents the formation of a malignant tumor.

*Anomaly of Pelvis.*—Papin<sup>4</sup> reported a case of anomaly of the pelvis in a man aged 40, with stenosis of the large calix, which had opened into an abnormal upper calix. The first symptom was an attack of pain in the right lumbar region, lasting several days, followed a year later by two similar, more severe attacks, each lasting several days, and accompanied by hematuria. Between the second and third attack, a pyelogram of the right side was made, which showed a large calix into which opened the greatly dilated lower calix through a markedly contracted orifice. After exposing the pelvis by a V-shaped incision in the two calices, prolonging the incision and creating a wide anastomosis between the calices, the patient had an uneventful recovery, and had had no further attacks of pain that had elapsed since the operation. Papin concludes that the case is unique in the literature on urology. The anastomosis was made very high, just below the ureter, making the procedure a difficult one. The operation may

4. Papin, Edmond: Sur un cas de bassinnet bifide avec communication du calice inférieur: Anastomose des deux grands calices, *Bull. Soc. Chir. Paris*, 1933.

more or less varied and ingenious methods that have been proposed and executed in cases in which there have been small hydronephrotic sacs.

*Horseshoe Kidney.*—Gutierrez<sup>5</sup> concluded, after a study of horseshoe kidney based on 25 cases, that this common congenital malformation is responsible for a definite clinical entity to which has been given the name "horseshoe kidney disease." The clinical manifestations of horseshoe kidney are due to the prominent position across the median line occupied by this anomalous kidney. The pressure of the organ on the great abdominal vessels, the celiac and lumbo-aortic plexuses, and the sympathetic and parasympathetic nerves which run along near the median line constitutes sufficient cause for a long-standing complaint. The threefold clinical expression consists in: first, intermittent attacks of indefinite abdominal pain, referred chiefly to the epigastric or umbilical region; second, marked chronic constipation, with or without gastrointestinal disorder, and third, urinary disturbances with early signs of chronic nephritis.

In many instances permanent cure or relief from symptoms cannot be obtained without surgical division of the isthmus by symphysiotomy. Although it appears that horseshoe kidneys do exist without causing symptoms, the fact remains that practically all persons with this anomaly who come for examination come because they are suffering with some chronic renal disease, due chiefly to the abnormal position of the fused organ and its excretory apparatus.

In Gutierrez's series of cases, the condition in 4 was found at postmortem examination and in 2, at operation; in 19 the diagnosis was made preoperatively by urologic and urographic methods. In all the cases there was much unknown and unsuspected pathologic change.

Horseshoe kidneys fall anatomically into two main groups: the symmetric and the asymmetric. The first of these, which alone is considered here, comprises two types: (1) kidneys fused by the lower poles and (2) those fused by the upper poles, the former condition being by far the most common. In either case, the fused organ is astride the spinal column at about the level of the third and fourth lumbar vertebrae, with all the characteristics of a horseshoe as regards its form. As a rule, the isthmus is composed of genuine renal parenchyma, and is seldom a band of fibrous tissue. In the usual type of horseshoe kidney the pelvis is anterior to the blood supply of the organ, with the ureters running before, and at times perpendicular to, the isthmus, and hence parallel to the vertebral column.

Before the era of pyelography, horseshoe kidney was found chiefly at necropsy, about once in 1,000 subjects. In the two decades of

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5. Gutierrez, R.: The Clinical Management of Horseshoe Kidney, *Am. J. Surg.* **14**:657 (Dec.) 1931; **15**:132 (Jan.) 1932; **15**:345 (Feb.) 1932.

systematic urologic examination, the ratio has risen to 1 in 400, and in any active urologic service it may be discovered in as high a proportion of pyelograms as 1 in 100 or 200. It is important to classify these cases into two groups: the cases in which, except for the anomaly, the kidney is normal but gives clinical symptoms, and the cases in which the kidney, in addition to being anomalous, is otherwise pathologic.

It is probable that fusion of the two organs occurs between the fifth and seventh weeks of embryonic life, as the result of some mechanical obstruction interfering with the normal upward migration and inward rotation of the two kidneys. Horseshoe kidneys are nearly always ectopic, and they retain the marked lobulation and furrows of the fetal organs on the anterior surface. The posterior surface is generally smooth, with a furrow in the isthmus formed by the passage of the great abdominal vessels. The hilus and the excretory apparatus are almost always ventrally and inwardly placed.

The organ, as a rule, is fixed, and it is the deep incarceration of the isthmus in the surrounding structures that is responsible for the clinical syndrome. The calices and pelves are markedly irregular in size, shape and position. Urographic studies reveal a peculiar, characteristic arrangement of the calices, especially the lowermost calices, in reverse position, looking inward toward the spinal column. The high implantation of the ureters results in mechanical obstruction at the ureteropelvic juncture, causing compression of the abdominal content by the overlying structure, resulting in retention, hydronephrosis, pyelonephrosis, and other renal diseases. Concomitant anomalies of other organs are very common.

The topographic relations of the blood, nerve and lymphatic supply have great significance here. The blood supply is nearly always anomalous, forming a network that contributes largely to the maintenance of the position of the organ. The intricate network of the sympathetic and parasympathetic nerves is responsible for the early nervous irritability, the continuous pressure of the weight of the isthmus on the exquisitely sensitive celiac plexus resulting in sudden pain and gastro-intestinal disorders. Obstruction of the lymphatic circulation by the pressure of the horseshoe kidney plays an important part in producing stagnation of lymph, resulting in symptoms of infection and disease of the organs of the retroperitoneal space. In addition, the parietal peritoneum lies directly on the isthmus (which lacks the perirenal fatty capsule) and is adherent to its anterior surface as well as to its excretory apparatus. Under these conditions, the intra-abdominal pressure and the weight and close relations of the organs bound together on it must interfere with the rhythmic dynamic contractions of the ureters, and must play a part in the marked stagnation of urine, which is characterized clinically



by intermittent attacks of pyelitis and pyelonephritis. As the early symptoms progress, the clinical picture may become aggravated through lack of drainage and through intense pyelonephritis, followed by recurrent attacks of fever, chills, general sepsis, ileus and uremia. The pressure of the renal mass on the aorta may lead to aortitis and aneurysm, with cardiac hypertrophy, thrombosis of the iliac veins and phlebitis.

The syndrome of horseshoe kidney was observed in 24 of the 25 cases reported. Every one of the patients had been examined previously in some other hospital, and various diagnoses had been made. Twelve of the patients (48 per cent) had been operated on elsewhere for various abdominal conditions, without obtaining relief.

It is chiefly urography that has made possible the preoperative diagnosis of horseshoe kidney. Pyelograms of both sides, whenever possible, or pyelograms made following intravenous injection are necessary, not only to verify the diagnosis, but to exclude the possibility of other abnormalities. As a further means of eliminating error, Gutierrez has established a new sign of distinct pathognomonic value, which he calls the "horseshoe kidney pyelographic triangle." This triangle has as its base the line joining the two lowermost calices in the pyelogram, and as its apex the point where the bisiliac line crosses the vertebral column. Owing to the abnormal approximation of these two calices in the horseshoe kidney, the basal angle is very narrow, ranging between 7 and 36 degrees, with an average of 20 degrees, in strong contrast with an angle of 90 degrees in a similar triangle drawn in normal kidneys.

The graphic points in the pyelogram for establishing a correct diagnosis of horseshoe kidney are: first, visualization and perfect outline of the position of the kidneys; second, possible delineation of the isthmus by roentgen rays; third, renal shadows of calculi close to the spinal column or overlapping it; fourth, in a pyelogram of both sides, rotation of the pelves; fifth, the lower calices pointing inward toward the median line; sixth, the "flower-vase" position of the ureters; seventh, the "bottle neck" shape at the ureteropelvic juncture, and eighth, the pathognomonic pyelographic horseshoe triangle, with its minimal basal angle of 20 degrees.

At the onset treatment should be conservative, but in most cases some surgical procedure is necessary later. Two types of cases must be considered: 1. Cases in which some concomitant associated pathologic change is present, and in which some type of surgical intervention may be required, as in any other pathologic lesions of the kidney. Obviously half of the kidney must have enough function to maintain life, particularly when heminephrectomy is to be carried out. 2. Cases in which no detectable pathologic change is present, but in

which, nevertheless, the syndrome of horseshoe kidney is clinically evident. Here renal symphysiotomy for the division of the isthmus of the fused kidney is the operative procedure of choice, followed by nephrolysis, ureterolysis and nephropexy. The best surgical method of approach has been found to be the retroperitoneal, since in this way peritoneal complications are entirely avoided. These operations on the horseshoe kidney are in reality conservative procedures, with good prognosis, relieving symptoms and achieving permanent cure.

Legueu and Fey<sup>6</sup> reported a case of horseshoe kidney. The pyelogram revealed four separate pelves; it was also obvious that the lower calices were placed in reverse, facing inward toward the median line, as though occupying the isthmus of the fused organ. The patient suffered from pain on the left side, where there was marked dilatation and infection. In view of the bilaterality of the lesion, which apparently caused one kidney to be superimposed on the other, and of the fact that there was evidence of only one ureter on each side, operation was not considered.

[COMPILERS' NOTE.—Another such unusual anomaly as a horseshoe kidney with four pelves has also been reported by Gutierrez.<sup>5</sup> There are perhaps 5 or 6 cases of this type on record. Before urography was possible, the condition was seldom, if ever, diagnosed clinically before operation. Nowadays it is easily and accurately diagnosed by means of ascending or descending pyelography. Accurate diagnosis has made it possible to anticipate complications and to diminish difficulties at the time of operation.]

Salleras<sup>7</sup> reported a case of horseshoe kidney, diagnosed pyelographically in advance of operation. If there is any reason to suspect the present of horseshoe kidney, the position of the ureters, pelves and calices should be carefully noted in the pyelogram. If the ureter enters the pelvis on the external margin of the latter, with marked deviation from the vertebral column, or if the pelvis is external with reference to the kidney, and the calices point toward the vertebral column, one may feel certain of the presence of this renal anomaly. Nevertheless, a horseshoe kidney with normal pyelographic characteristics may occur if the kidneys have ascended to a fairly normal position. In the case reported, there was pyonephrosis of the left kidney, for which nephrectomy was done.

A pyelogram of both sides revealed that the left ureter, of normal size, deviated strongly outward and was widely separated from the

6. Legueu and Fey: *Pyélographie d'un rein en fer à cheval*, *J. d'uro.* **27**:347 (March 18) 1929.

7. Salleras, Juan: *Riñón en herradura con pionesrosis del izquierdo*. Diagnóstico pielográfico. Nefrectomía. Curación, *Rev. Asoc. méd. argent.* **46**:1287 (Oct.) 1932.

vertebral column. The left renal pelvis, much distended, was four times its normal size and occupied an inverted position. The calices situated within the pelvis, although inverted, were projected in the pyelogram against the transverse processes of the first to the fourth lumbar vertebrae; at the fourth there was a prolongation of the lowermost calix, which was dilated and possibly corresponded to the isthmus of the horseshoe organ. The right ureter followed a normal course and was not enlarged. The image of the two kidneys, taken together, gave the impression of a horseshoe kidney joined at the lower poles, which finding, together with left pyonephrosis, was confirmed at operation.

Salleras made his incision slightly within the parenchyma of the left kidney, to form a stump for the ligature. A large quantity of pus gushed out, and a kidney three times the normal size was found, with its fatty capsule closely adherent to the capsule proper. When the removed specimen was opened through its convex border, it was found that the parenchyma had almost entirely disappeared, being replaced by enormous cavities which were the site of pyonephrosis.

*Formation of Calculi.*—Gottstein<sup>8</sup> stated that definite progress has been made in the study of urinary calculi, as to the etiology, pathology, diagnosis and treatment. Recent years have produced good experimental work on oxalate, urate and phosphate stones. These studies have aided the work on the etiology of formation of stones. Endoscopic technic has enhanced diagnosis, especially in association with simple roentgen rays and pyelography. Conservative methods have displaced surgical methods in the treatment of ureteral calculi, especially with small stones. With kidney stones, Gottstein stated that one must still depend on operation; this will probably remain the method of choice unless newer methods are forthcoming. The author concluded that radical methods should be used only when the investigator believes that conservative methods may lead to recurrence.

Ewell<sup>9</sup> stated that cystine stones of the kidney occur as complications of cystinuria; the latter, in all probability, is due to an error in metabolism, with a definite hereditary tendency.

This formation of stones is dependent on different factors, such as stasis and infection, and should be suspected in all cases in which renal calculi are recurrent; the calculi and urine should be examined chemically for cystine. If a cystine stone is found, or if cystinuria is demonstrated, the patient should be given a diet low in protein. Proteins containing a large amount of cystine are to be avoided, and the urine should be rendered alkaline by internal administration of alkalis. After three months of such care in 2 of Ewell's cases, sandy particles

8. Gottstein, G.: Nieren-und Uretersteine, Beitr. z. klin. Chir. 156:315, 1932.

9. Ewell, G. H.: Cystine Nephrolithiasis, J. A. M. A. 99:2160 (Dec. 24)

of cystine and crystals disappeared from the urine, with a decrease in the concentration of cystine in the urine. Crystals promptly returned after resumption of a general diet and discontinuance of the alkali. The possibility of the formation of phosphatic calculi from the intake of alkali should be borne in mind. In Ewell's case 3, conclusions were not warranted. In case 4, the formation of calculi was not prevented after several months of apparently the same care.

Young<sup>10</sup> stated that the subject of recurrence after operation for renal and ureteral calculi is very important, for the great clinics of the country have reported recurrence in from 20 to 40 per cent of cases. He stated briefly that the cause of recurrence is one of the following: missing a calculus or leaving a fragment, persistent infection, dependent or badly draining calices or pouches or obstructions at the ureteropelvic juncture. If the stone lies within a calix or pouch which has excellent drainage, removal of the stone by pyelotomy usually will be the method of choice, and can be expected to give good results, if one is careful to sterilize the urine before allowing the patient to leave. If the infecting organism is a coccus, neoarsphenamine, in doses from 0.30 to 0.75 Gm. intravenously, at intervals of from three to four days, usually will give quick results. With bacillary infections, it is more difficult to obtain sterilization, and various treatments by mouth and intravenously may be required in addition to pelvic lavage.

When the stone is in a dependent pouch, and drainage is uphill, especially if the infundibulum leading from the pouch to the pelvis is contracted, the stone usually cannot be removed by pyelotomy. In preference to nephrotomy, Young generally carries out resection of the pole of the kidney, unless contraindications exist. Young proposed this method a number of years ago for use in cases of this character, and has been greatly pleased with the results obtained. He recently studied 17 cases, in 14 of which the lower pole had been resected, and in 3, the upper pole. There has not been a single recurrence of renal or ureteral calculus in any of these cases. He expressed the belief that the operation is greatly to be preferred to extensive nephrotomy, which leads to marked destruction of renal tissue from the multiple sutures that are required to stop bleeding. By thus removing the stone-bearing area and the poorly draining pocket, if one continues to treat the patient until sterile urine is obtained, calculi will, in Young's opinion, rarely recur.

Randall<sup>11</sup> stated that alkalinization and phosphatic encrustations can be prevented by lavage of the bladder with phosphoric acid post-

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10. Young, H. H.: Discussion, *Tr. Am. A. Genito-Urin. Surgeons* 25:152, 1932.

11. Randall, Alexander: Problem of Recurrent Renal Calculi with the Consideration of a New Preventive Treatment, *Tr. Am. A. Genito-Urin. Surgeons* 25:123, 1932.

operatively. Treatment of staphylococcic cystitis, leukoplakia and allied conditions by this means is indicated. There has been every indication of success in the prevention of recurrent renal calculi of the phosphatic variety. The recognized action of such strengths of phosphoric acid in vitro and the tolerance to such topical applications in vivo make possible the dissolution of small phosphatic calculi or of fragments left at operation.

Randall concluded that as this means of treatment has proved safe and efficacious in renal operations as a postoperative prophylactic measure against infection with the alkali-producing organisms, it should aid in the prevention of recurrent renal calculi of the phosphatic variety.

*Polycystic Disease.*—Noszkay<sup>12</sup> stated that it has not been definitely decided whether polycystic kidney is a disturbance in the development of the kidney or a tumor. However, such factors as heredity, bilaterality and similar processes in other organs tend to cause one to attribute the condition to developmental disturbances. Degeneration of a polycystic kidney is progressive, and leads to complete renal insufficiency and, finally, uremia.

The diagnosis of early polycystic kidney is difficult, since there are no characteristic symptoms. However, bilateral pyelography is a great aid because of the characteristic pyelograms. Since polycystic kidney is a progressive disease, treatment should be as conservative as possible. The progress of the condition cannot be deterred by operation, and there will be only temporary symptomatic relief, such as cessation of hematuria, diminution in the size of the tumors and passive increase in renal function. For this, Payr's cystic puncture is advocated.

A polycystic kidney should be removed only if there is a vital indication, and if the other kidney is functionally capable and there is no danger of oncoming uremia. Such indications may be continuous hematuria or renal infection. In the case of a unilateral renal tumor, if the diagnosis is undecided, exploration is warranted.

Braasch and Schacht<sup>13</sup> collected data on 193 patients observed at the Mayo Clinic for whom a diagnosis of polycystic kidney had been made. At the time of the onset of symptoms, the average age of the patients was 38.8 years. The average length of life of the patients who were reported to have died was fifty years. There was definite evidence of a hereditary trend. A systolic blood pressure of 145 mm. of mercury, or more, was found in 61 per cent. of the cases; the diastolic blood

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12. Noszkay, Aurel: Ueber die polycystische Niere, *Ztschr. f. urol. Chir.* **35**:238, 1932.

13. Braasch, W. F., and Schacht, F. W.: Pathologic and Clinical Data Concerning Polycystic Kidney, *Tr. Am. A. Genito-Urin. Surgeons* **25**:85, 1932.

pressure was more than 90 mm. in 55 per cent, and more than 95 mm. in 47 per cent. Peripheral sclerosis was observed in 15.4 per cent. Retinal sclerosis, with other ocular changes, was noted in 51 per cent. Laboratory evidence of renal insufficiency was present in more than 60 per cent. Surgical complications occurred in approximately 20 per cent of the cases; this is a larger percentage than is usually recorded.

Braasch and Schacht stated that renal polycystic disease is easily overlooked, and usually is overlooked in the course of general clinical examination, since there are often no symptoms present which would indicate renal involvement. The failure to discover that renal enlargement is bilateral may lead to the erroneous diagnosis of renal neoplasm. Bilateral urographic studies may be necessary to determine involvement of both kidneys when abdominal palpation reveals unilateral enlargement. The most common symptom is a dull pain, usually referred to either renal region. The first clinical symptoms are frequently those of renal insufficiency, although a remarkable degree of tolerance is often noted in the presence of advanced renal destruction. Laboratory evidence of marked reduction in renal function, with comparatively few subjective symptoms, in the case of an adult who is in the third or fourth decade of life, should call attention to the probability of polycystic renal disease. The prognosis will vary largely with the degree of renal dysfunction. If renal function remains normal, the prognosis is good. Even moderate reduction of renal function may remain stationary for as many as ten or fifteen years. When the reduction is advanced, the prognosis becomes grave, although several years may elapse before death. Expectancy of life will average almost fifty years, although patients are frequently observed who are more than 60 years of age. The hereditary nature of the disease should discourage the having of progeny, and sterilization should be advocated.

*Hydronephrosis.*—König<sup>14</sup> reported 7 cases of intermittent hydronephrosis in which careful examination was made to determine the cause of the pelvic obstruction. In 2 cases the obstruction was caused by inflammatory bands; in 4, by accessory vessels, and in 1 case by a combination of these. In 4 cases it was necessary to perform nephrectomy. In 3 cases, satisfactory results were obtained by freeing the ureter, cutting through the accessory vessels and removing the obstructing bands. In 2 cases, cure resulted from the clearing up of associated infectious pyelitis.

König stated that it is always essential to remember the possibility of anomalous blood vessels as a cause of hydronephrosis.

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14. König, F.: Ueber intermittierende Harnstauung im Nierenbecken, Deutsche Ztschr. f. Chir. 227:326, 1930.

Walters<sup>15</sup> stated that the return of renal function after removal of obstructing lesions seems rather remarkable. If one is to attempt to preserve a kidney injured as the result of an obstructing lesion when the other kidney is normal, one must have sufficient evidence that such a kidney will return to reasonable function after relief of obstruction and after control of infection, rather than to a decrease in function and to atrophy.

Walters expressed the belief that a most important point in such a decision is the amount of renal parenchyma that is present, as measured by the thickness of the cortex and the size of the calices. Even in cases in which a good deal of infection appears to coexist with the obstructing lesion, in the presence of small cortical abscesses, the kidney may free itself of such infection after relief of the urinary obstruction. In such cases, removal of the fibrous capsule of the kidney, enabling the cortical infection to discharge itself, should be a part of the procedure. In the presence of stones in the kidney and ureter, estimations of renal function, such as excretion of phenolsulphonphthalein, indigo carmine and various mediums used in intravenous urography, do not give accurate indexes of renal function. If this is the case, whenever sufficient renal parenchyma remains, the kidney should not be removed until sufficient evidence accumulates, after removal of the obstruction, that the kidney is not functioning. Indications for conservative procedures, such as resection of the renal pelvis, reimplantation of the ureter or removal of obstructions, such as peripelvic tissue, are strikingly indicated when the hydronephrosis is bilateral or, if it is unilateral, when sufficient renal parenchyma remains to justify its preservation. In making the decision as to the best conservative treatment to follow in hydro-nephrosis, one should be guided by one's own experience, remembering that the safest and best procedure is the one which produces adequate and complete relief from the obstruction, with only disturbance of the renal pelvis or ureteral tissue.

*Tuberculosis.*—Thomas and Kinsella<sup>16</sup> have come to the conclusion that successful surgical treatment of urogenital tuberculosis depends primarily on accurate diagnosis. This may be accomplished only after repeated, complete urologic examinations. Surgical treatment for any type of tuberculosis, except in an emergency, should not be undertaken until the patient has developed a sufficient defense mechanism. Urogenital tuberculosis rarely demands emergency operation. Any such treatment of tuberculosis, surgical or medical, should aim at treatment of the patient as a whole and not just the local lesion. The authors

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15. Walters, Waltman: Restoration of Renal Function Following Removal of Obstructing Lesions, *Ztschr. f. urol. Chir.* **36**:264 (Jan.) 1933.

16. Thomas, G. J., and Kinsella, T. J.: Modern Aspects of the Surgical Treatment of Urogenital Tuberculosis, *Tr. Am. A. Genito-Urin. Surgeons* **25**:405, 1932.

said that nondestructive renal tuberculosis, unilateral or bilateral, is a nonsurgical condition and should be treated intensively by medical methods. Unilateral, slightly destructive tuberculosis should be treated conservatively under careful observation. Nephrectomy is indicated only when progressive disease is present. Extensive unilateral destructive lesions should be treated by surgical methods. In bilateral destructive renal tuberculosis an operation is not indicated except when it is necessary to stop hemorrhage or to relieve pain and infection, the result of an obstructed ureter.

Thomas and Kinsella stated that genital tuberculosis is usually an infection of the prostate gland and epididymis, and in a high percentage of cases is associated with a renal lesion. They stated that tuberculosis of the epididymis is often an acute disease, and can be cured by drainage and heliotherapy. When an operation is necessary, it should be an epididymectomy and not an orchidectomy. Surgical treatment of tuberculosis does not cure the disease, but it mechanically aids in producing a clinical result. Constitutional treatment of urogenital tuberculosis is important and should supplement surgical treatment, both before and after operation.

*Carbuncle.*—Patch and Reid<sup>17</sup> reported 2 fatal cases of bilateral renal carbuncle, in both of which the diagnosis was proved at necropsy. In 1 of the cases there was a typical carbuncle of the liver. Two other cases of presumable renal carbuncle with perinephritic abscess were reported; both patients recovered following drainage of the abscess.

The authors stated that the value of a pyelogram in arriving at a diagnosis was demonstrated in the two cases of presumed renal carbuncle. Early diagnosis and conservative treatment are two important factors, and should be emphasized. They expressed the belief that in all obscure cases, even when only slight signs and symptoms suggest involvement of the urinary tract, full urologic study should be made.

O'Connor also reported 2 instances of renal carbuncle, in both of which the left kidney was involved. Both cases were correctly diagnosed before operation. Diagnosis was made possible by roentgenologic studies, coupled with the history and clinical examination. Complete recovery followed nephrectomy. As near as O'Connor was able to ascertain, this report brings the total to 94 reported cases.

*Cysts.*—Pfaehler<sup>18</sup> reported a case of bilateral solitary cyst of the kidney. Both cysts were the size of a child's head, and were successfully enucleated from the kidney, the first in 1923 and the second six years later. The patient made a good recovery.

17. Patch, F. S., and Reid, R. G.: Carbuncle of the Kidney, *Tr. Am. A. Genito-Urin. Surgeons* 25:1, 1932.

18. Pfaehler, P.: Beitrag zur Frage der doppelseitigen Solitär-cystenbildung der Niere, *Ztschr. f. urol. Chir.* 36:224 (Jan.) 1933.



*Infarcts.*—Barney and Mintz<sup>19</sup> have gone over the records of necropsy of the Massachusetts General Hospital and have found and studied 143 cases of infarct of the kidney. Of this series, 117 patients (83 per cent) were admitted to the medical wards, and only 22 to the surgical service. Of the latter, 6 were admitted with gangrene of one or both legs, and amputation was performed; 9 had a more or less acute abdominal condition; 3 came because of carcinoma, and 3 others for empyema.

Most of the patients admitted to the medical service were found to have acute or chronic heart disease, many with decompensation; the chief cause of illness of the others was marked arteriosclerosis. Of the patients with infarct, 57.5 per cent were males. The youngest patient was a boy, 6 years of age; the oldest a man, 77 years of age. However, the great majority were between 30 and 50 years of age; more than 24 per cent were from 30 to 40 years, and more than 19 per cent from 40 to 50 years of age. Infarcts of the kidney, then, are most commonly seen at the prime of life.

In about 38 per cent of this series Barney and Mintz found the urine persistently normal. In 80 cases (61 per cent), in which the urine was not normal, it was often doubtful whether the presence of infarction of the kidney accounted for the pathologic condition found. Only about 10 (9 per cent) of the patients complained of urinary symptoms, such as frequency, difficulty or dysuria. Four of the 10 patients were those who were mentioned as having hematuria. The remaining 116 (91 per cent) made no complaint of urinary symptoms. In 88 cases (64.7 per cent) there was no history of pain or tenderness.

At postmortem examination a normal heart, including the myocardium and valves, was found in only 6 (4.4 per cent) of 136 cases in which the observation was recorded. In 130 cases (about 95 per cent) the heart and its valves showed changes of greater or lesser extent. In 92 cases of this group (67.6 per cent) the lesions were of long standing, associated in a great many cases with arteriosclerotic changes.

Barney and Mintz found pathologic conditions in the lungs in 71 cases (55 per cent). Of these, infarctions were most frequent; there were infarctions in 34 cases (26.9 per cent), with pneumonia next in order of frequency (17 cases). Abscesses, pulmonary emboli, hydrothorax and empyema were observed in several instances in one or another combination with the infarction.

Barney and Mintz also found that both kidneys were the seats of infarcts in 77 cases (54.2 per cent); 3 of these cases were included among the 5 cases of total infarct already mentioned. Streptococci,

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19. Barney, J. D., and Mintz, E. R.: *Infarcts of the Kidney*, J. A. M. A. 100:1 (Jan. 7) 1933.

generally *Streptococcus viridans*, were the offending organisms in 40 cases (72.7 per cent of the positive cases), staphylococci coming next in 10 instances (18.1 per cent). The great predominance of infections of the cardiac valves would seem, therefore, to coincide with the high incidence of streptococci.

*Abscess.*—Casco<sup>20</sup> reported a case of renal amebic abscess, affecting a boy 4 years old, which was evacuated spontaneously by way of the urinary passages. The case was unusual, both on account of the place where the abscess formed, and also because of its evolution. The child was a native of Corrientes (Argentina) where amebiasis is endemic. His illness began with diarrhea, and he was brought to the clinic in a state of extreme malnutrition. As *Endamoeba* was found in his stools, he was treated with emetine hydrochloride, and apparently made a good recovery. He was brought back by his father five months later, however, in a state of undernourishment, with a distended abdomen; the left kidney was enlarged and painful on palpation. Although diarrhea was not present, examination disclosed a few amebic cysts in the stools. The urine contained abundant pus and cells of the vesical epithelium. A few days later, when blood was found in the urine, the patient was admitted to the hospital. On the second day he passed large quantities of pus in the urine and many amebic cysts. Although hope of recovery seemed slight, treatment with emetine hydrochloride was instituted, following which the child recovered; he had remained well up to the time of the writing of the report.

While the dosage given was large for a young and undernourished child, Casco expressed the belief that this is the only way to make the parasite disappear.

*Fistula.*—Barnes<sup>21</sup> reported a case of renocolic fistula. This resulted from neglected calculous pyonephrosis with rupture into the ascending colon. A diagnosis was made by means of a pyelogram, which showed the escape of the pyelographic fluid into the cecum. Nephrectomy and closure of the opening into the cecum were successfully accomplished.

Barnes expressed the belief that this case emphasizes the importance of earlier urologic study in cases of continued pyuria. It also adds another interesting condition to the list of sequelae of neglected pyonephrosis.

*Function.*—Janney and Walker<sup>22</sup> stated that they had presented the results of a test designed to show the peak capacity of the kidney

20. Casco, E. D.: Absceso amebiano de riñón eliminado por vías naturales, *Rev. méd. latino-am.* **17**:1165 (May) 1932.

21. Barnes, R. W.: Acquired Reno-Colic Fistula, *J. Urol.* **29**:111 (Jan.) 1933.

22. Janney, J. C., and Walker, Elisabeth W.: Kidney Function in Pregnancy: Water Diuresis in Normal Pregnancy, *J. A. M. A.* **99**:2078 (Dec. 17) 1932.

to dispose of water, and that they had shown that this capacity declines progressively among clinically normal pregnant women in the last twelve weeks of pregnancy. It has already been shown that fever reduces the volume of urine, and the conjunction of intercurrent disease with this lowered functional capacity of the kidney in the later weeks of pregnancy has been considered as a precipitating factor in toxemic states. The results of this test in a small group of patients with toxemia have been reported, and the clinically well known urinary retention which occurs in this condition has been demonstrated by this method.

*Infection.*—Preiss<sup>23</sup> stated that in the last forty years more than 240 cases of mechanical ileus in pregnancy have been reported. In 34 of these cases necropsy was performed and revealed true ileus of pregnancy, that is, ileus caused by the pressure on the intestine of a normal, gravid uterus. In 9 of the 34 cases there was associated pyelitis of pregnancy.

A case of a primigravida, aged 23, who had true ileus of pregnancy is reported. This patient had had two operations before pregnancy, and chronic pyelitis in the course of it. Between the fifth and sixth months the infection became more severe; ileus developed which did not respond to ordinary measures of treatment and rapidly became worse. Laparotomy disclosed the presence of ileus; the uterus was emptied, and the woman recovered.

There are several explanations of ileus of pregnant women: intestinal paralysis secondary to the toxicosis of severe pyelitis, ileus resulting in traction of the pregnant uterus on the vaginal neck, retroperitoneal phlegmonous infection following pyelitis, intestinal atony from the toxins of pregnancy and pressure on the dilated intestines by the uterus. Treatment of this condition is laparotomy and emptying of the uterus; the pyelitis by itself is not sufficient indication to interrupt pregnancy unless it is associated with a high degree of ileus.

Wegelin<sup>24</sup> described a case of aspergillosis of the kidney affecting a man, aged 56, who otherwise was healthy. The kidney was removed, and the wound healed rapidly. The fungus growth caused definite necrosis, which was limited to the renal parenchyma; however, in the remainder of the kidney there was a definite chronic inflammatory reaction. Microscopic examination revealed caseous-cavernous destruction of a portion of the kidney. Infection resulted from the hematogenous transmission of the spores; it was impossible to determine the point of entry.

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23. Preiss, Hans: Ueber Pyelitis gravidarum und Ileus, *Zentralbl. f. Gynäk.* 57:319 (Feb. 11) 1933.

24. Wegelin, C.: Ueber eine Schimmelpilzerkrankung der menschlichen Niere, *Ztschr. f. urol. Chir.* 36:281 (Jan.) 1933.

## PARARENAL TUMORS

Quénu<sup>25</sup> observed a woman, aged 42, suffering from a condition that should be classified as pararenal tumor as defined by Lecene in 1919, since it fulfils all the anatomic and pathologic conditions suggested by Lecene. The kidney was preserved and was left intact after removal of the tumor.

Study of the late results in these cases is interesting in view of the paucity of reports on the subject. In reports of 65 cases that Lecene reviewed in which the patients had survived operation, he found only 15 in which the patients had been traced for more than one year. In Quénu's case the patient had no recurrence until three years after operation. The secondary growth, when it developed, was not on the flank, as was the primary tumor, but above in the hypochondrium and below in the pelvis, as if several nodules had been left at each pole. These secondary growths were removed without difficulty. There was another recurrence eighteen months later, this time at the site of the original tumor. Quénu accordingly opened the abdomen for the third time, one year previous to the writing of his report. This time the operation was more difficult, and in an attempt to preserve the kidney part of the parenchyma was resected. Quénu has seen the patient three times since, and at the time of writing she had a small pelvic nodule to the right of the uterus, which may have been a third recurrence. Her general condition continued to be good.

Lepoutre<sup>26</sup> stated that the diagnosis of paranephritic tumor is rarely made before operation. Evolution of the tumors suggests the reason for this: If they are large, they tend to develop abdominally, and the surgeon does not think of a paranephritic tumor. A pyelogram, however, reveals the condition readily. Histologic examination of the tumor is generally of interest, for there are usually several tumors, and the structure may be entirely different. Thus, in one of the cases the pathologist had made the diagnosis of lipoma, but there was rapid recurrence, and the second histologic examination disclosed that one of the masses removed was a fibroma, and the others were sarcomatous, although one seemed to be lipomatous. This proves that all the masses should be examined separately if an accurate and complete diagnosis is to be made.

Two of the tumors in Lepoutre's series were of the fatty capsule, and could be separated from the kidney only by decapsulation. In one of these, the vessels were seen to pass from the tumor into the adjacent parenchyma. This made it desirable to remove the kidney and tumor

25. Quénu, Jean: Un cas de tumeur solide paranéphrétique trois fois opéré, *Bull. et mém. Soc. nat. de chir.* 58:1247 (Oct. 19) 1932.

26. Lepoutre, C.: Sur trois cas de tumeurs paranéphrétiques, *Bull. et mém. Soc. nat. de chir.* 58:1389 (Nov. 16) 1932.

in a single piece, although this is not always possible. Good results are not easily obtained, yet Lepoutre had a case of sarcoma in which the patient survived for five years after an operation of this kind. In his first case, there was recurrence a month after extensive resection. Recurrences are common in these cases and should always be considered.

#### SUPRARENAL TUMORS

Bleicher<sup>27</sup> stated that suprarenalectomy is today regarded as a delicate and dangerous operation, because of the deep situation of the organ, its small size, its friability, its close relation to the renal pedicle and great vessels of the abdomen and the thickness of its adipose covering. The old technics were based on old and faulty concepts of anatomy, and therefore gave incomplete results.

Bleicher's technic, based on dissection of more than 100 cadavers, is essentially anatomic. He uses the retroperitoneal route and removes preferably the left gland when the choice is free. The transperitoneal route is employed only for suprarenal tumors or for considerably enlarged glands. His technic is satisfactory for suprarenalectomy, medullosuprarenalectomy, suprarenal enervation, removal of suprarenal cysts and operation on either gland.

With the patient in the right lateral decubitus position (for operation on the left gland), and with a pillow in the hollow of the thorax at the waist to keep the viscera from being crowded into the operative field, the abdominal wall is incised, with the center of the wound corresponding to the middle part of the ninth rib, high enough and anterior enough for an approach, not oblique, but normal, to the antero-exterior aspect of the gland. It is a parietal curvilinear incision, grazing the margin of the rib. The cutaneous incision starts at the external margin of the sacrolumbar mass, that is, from 6 to 8 cm. from the crest of the ilium. It follows the longitudinal axis of the twelfth rib, and when it arrives at the free extremity of the rib, turns upward to follow, at a distance of 1 cm., the lower border of the thorax, ending near the axillary line. It involves the entire thickness of the subcutaneous tissue. Section of the superficial muscular layers follows the line of the cutaneous incision; the latissimus dorsi muscle is sectioned backward, and the posterior portion of the obliquus externus muscle, forward. In sectioning the median layer of muscles, the incision of the serratus posterior inferior is made backward, and that of the posterior margin of the obliquus internus, forward. Subperiosteal resection of the twelfth rib follows, after longitudinal incision of its periosteum. The deep muscle layer is cut transversely, at the level

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27. Bleicher, M.: *Technique opératoire de la surrénalectomie basée sur l'anatomie*, Arch. franço-belges de chir. **33**:97 (Feb.) 1932.

of the anterior part of the incision, to respect the eleventh intercostal nerve, which, with the intercostal vessels of the eleventh intercostal space, is drawn upward with the superior lip of the incision by the tenaculum. The twelfth nerve is similarly hooked downward with the lower lip.

The perirenal capsule is now seen through the transverse and retroperitoneal fascia that have been exposed by section of the transverse muscle. The kidney is identified through its fibro-adipose envelop; the retrorenal fascia is incised vertically, from above downward, a little within and behind the renal margin, as it is made out. The partition between the kidney and the suprarenal gland must now be broken through to the edge of its insertion on the prerenal fascia. When the tip of the hand inserted in the renal *loge* reaches the vicinity of the internal edge of the kidney, the fatty prerenal bed is broken down. This must be done tangentially to the prerenal fascia, obliquely from above downward, and from without inward, for the entire length of the renal margin. When the wall is broken down, separation of the presuprarenal fascia is easy; it should be done deeply, down to the side of the vertebral column, the outline of which is felt. A retractor is introduced to pull the upper part of the fascia strongly forward. This method makes it possible to respect the peritoneum completely, the surgical manipulation being always separated from it by the prerenal fascia.

The upper lip of the wound is drawn strongly upward; an assistant draws the kidney strongly backward, with his hand introduced into the renal space, which is now stretched open wide. This brings the antero-exterior aspect of the gland into full view.

To avoid hemorrhage, one should separate the gland from the kidney with curved scissors that have blunt points; the fat separating them is strongly adherent to the gland but not to the kidney; the gland should, therefore, be separated in this way as far as the muscular layer of the posterior abdominal wall, the scissors going from without inward, to the internal edge of the gland, passing behind the retro-suprarenal cushion, where cleavage is easy.

The gland is now held in place only by its vascular and nerve pedicle, included in a continuous nap of cellulo-adipose tissue. To remove the gland, two elbowed clamps are placed parallel to each other on the superior vascular pedicle at the top of the gland, with room between them for scissors to pass, and two others are placed similarly parallel on the inferior pedicle, near the lower end of the organ, as far as possible from the renal vessels. Care must be taken that the clamps will include the entire thickness of the connective tissue and vascular nap. These pedicles are now cut, leaving as the only support the middle vascular and nerve pedicle, inserted on its internal edge. The

organ is now tilted forward, the middle pedicle playing the part of a hinge. This pedicle is clamped and cut along the margin of the gland, with the same precaution as the others. The pedicles are ligated with catgut, or buried metal hooks can be used if preferred. The abdomen is closed in layers, with or without drainage. It is unnecessary to fix the kidney in its bed, for this organ shows no tendency to leave its place.

*(To be Continued)*

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